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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07K 14/115, 14/135, 14/155, 14/16, A61K 38/16, A61P 31/12		A1	(11) International Publication Number: WO 00/69902 (43) International Publication Date: 23 November 2000 (23.11.00)
(21) International Application Number: PCT/US00/13651 (22) International Filing Date: 17 May 2000 (17.05.00) (30) Priority Data: 60/134,406 17 May 1999 (17.05.99) US 60/153,406 10 September 1999 (10.09.99) US (71) Applicant (for all designated States except US): CONJUCHEM, INC. [CA/CA]; Suite 3950, Third Floor, 225 President Kennedy Avenue West, Montreal, Quebec H2X 3Y8 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): BRIDON, Dominique, P. [FR/CA]; 243, chemin Cote Sainte-Catherine, Outremont, Quebec H2V 2B2 (CA). DUFRESNE, Robert, P. [-/US]; 115 Pilgrim Road, Wellesley, MA 02181 (US). BOUDJELLAB, Nissab [-/CA]; 420 Bourke, Apt. 2A, Dorval, Quebec J5A 2M1 (CA). ROBITAILLE, Martin [-/CA]; Conjuchem, Inc., Suite 3950, Third floor, Montreal, Quebec H2X 3Y8 (CA). MILNER, Peter, G. [GB/US]; 14690 Manuella Road, Los Altos Hills, CA 94022 (US). (74) Agents: WARD, Michael, R. et al.; Limbach & Limbach L.L.P., 2001 Ferry Building, San Francisco, CA 94111-4207 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: LONG LASTING FUSION PEPTIDE INHIBITORS OR VIRAL INFECTION			
(57) Abstract <p>Peptides exhibiting anti-viral and anti-fusogenic activity are modified to provide greater stability and improved half-life <i>in vivo</i>. The selected peptides include fusion inhibitors DP178 and DP107 and related peptides and analogs thereof. The modified peptides are capable of forming covalent bonds with one or more blood components, preferably a mobile blood component.</p>			

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LONG LASTING FUSION PEPTIDE INHIBITORS OF VIRAL INFECTION

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FIELD OF THE INVENTION

This invention relates to modified peptides that are inhibitors of viral activity and/or exhibit antifusogenic properties. In particular, this invention relates to modified peptide inhibitors of human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), human parainfluenza virus (HPV), measles virus (MeV), and simian immunodeficiency virus (SIV) with long duration of action for the treatment of the respective viral infections. The invention also relates to conjugates of the modified peptides and endogenous carriers, particularly conjugates of the modified peptides and various mobile blood components, particularly mobile endogenous proteins.

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BACKGROUND OF THE INVENTION

Membrane fusion events, while commonplace in normal cell biological processes, are also involved in a variety of disease states, including, for example the entry of enveloped viruses into cells. Peptides are known that inhibit or otherwise disrupt membrane fusion-associated events, including, for example, inhibiting retroviral transmission to uninfected cells. As an example, the synthetic peptides DP-107 and DP-178 derived from separate domains within the human immunodeficiency virus type 1 ("HIV-1") transmembrane ("TM") glycoprotein gp41, are potent inhibitors of HIV-1 infection and HIV induced cell-cell fusion.

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Lambert, et al., "Peptides from Conserved Regions of Paramyxovirus Fusion (F) Proteins are Potent Inhibitors of Viral Fusion," Proc. Natl. Acad. Science U.S.A., March 5, 1996, Vol. 93 (5), pp. 2186-91, discloses that the synthetic peptides DP-107 and DP-178 (T-20), derived from separate domains within the human immunodeficiency virus type 1 (HIV-1) transmembrane (TM) protein, gp41, are potent inhibitors of HIV-1 infection and fusion. Using a

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computer searching strategy (computerized antiviral searching technology, C.A.S.T.) based on the predicted secondary structure of DP-107 and DP-178 (T-20), Lambert, et al. identified conserved heptad repeat domains analogous to the DP-107 and DP-178 regions of HIV-1 gp41 within the glycoproteins of other
5 fusogenic viruses. Antiviral peptides derived from three representative paramyxoviruses, respiratory syncytial virus (RSV), human parainfluenza virus type 3 (HPIV-3), and measles virus (MV) blocked homologous virus-mediated syncytium formation and exhibited EC_{50} values in the range 0.015-0.250 μ M. Moreover, these peptides were highly selective for the virus of origin.

10

U.S. Patent Nos. 6,013,263, 6,017,536 and 6,020,459 incorporated herein in their entirety, likewise disclose that the 36 amino acid peptide DP178 corresponding to amino acids 638 to 673 of gp41 from the HIV-1 isolate LAI (HIV-1_{LAI}), and the 38 amino acid peptide DP107 corresponding to amino acids
15 558-595 of gp41 from the HIV-1_{LAI}, both exhibit potent anti-HIV-1 activity.

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While many of the anti-viral or anti-fusogenic peptides described in the art exhibit potent anti-viral and/or anti-fusogenic activity, these peptides suffer from short plasma half-lives *in vivo*, primarily due to rapid serum clearance and
20 peptidase and protease activity. This in turn greatly reduces the effective anti-viral activity of the peptides. There is therefore a need for a method of prolonging the half-life of existing anti-viral and/or anti-fusogenic peptides and providing for longer duration of action of these peptides *in vivo*.

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SUMMARY OF THE INVENTION

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The present invention meets these and other needs and is directed to modified peptides having anti-viral activity and/or anti-fusogenic activity. These modified peptides provide for an increased stability *in vivo* and a reduced susceptibility to peptidase or protease degradation. These modified peptides
30 thereby minimize, e.g., the need for more frequent, or even continual,

administration of the peptides. The products of varying embodiments of the present invention can be used, e.g., as a prophylactic against and/or treatment for infection of a number of viruses, including human immunodeficiency virus (HIV), human respiratory syncytial virus (RSV), human parainfluenza virus (HPV), measles virus (MeV) and simian immunodeficiency virus (SIV). Modification of other peptides involved in viral transfection (e.g., Hepatitis, Epstein Barr and other related viruses) is also within the scope of the invention.

This invention relates to chemically reactive modifications of peptides exhibiting anti-viral and/or anti-fusogenic activity such that the modified peptides can react with available functionalities on blood components to form stable covalent bonds. In one embodiment of the invention, the modified peptides comprise a reactive group which is reactive with amino groups, hydroxyl groups, or thiol groups on blood components to form stable covalent bonds. In another embodiment of the invention, the reactive group can be a maleimide which is reactive with a thiol group on a blood protein, including a mobile blood protein such as albumin.

In particular, the invention relates to such chemically reactive modifications of DP107 and DP178 peptides and analogs thereof, including peptides comprised of amino acid sequences from other (non-HIV) viruses that correspond to the gp41 region of HIV from which DP107 and DP178 are derived and that exhibit anti-viral or anti-fusogenic activity. More particularly, these peptides can exhibit anti-viral activity against, among others, human respiratory syncytial virus (RSV), human parainfluenza virus (HPV), measles virus (MeV) and simian immunodeficiency virus (SIV). The invention also relates to such chemically reactive modifications of the peptides of SEQ ID NO:1 to SEQ ID NO:86.

The invention also relates to compositions for use in the prevention and/or treatment of viral infection comprising a peptide that exhibits anti-viral activity modified with a reactive group as described. More particularly, the invention relates to such compositions for use in the prevention and/or treatment of AIDS,

human respiratory syncytial virus (RSV), human parainfluenza virus (HPV), measles virus (MeV) and simian immunodeficiency virus (SIV).

BRIEF DESCRIPTION OF THE TABLES

5 The invention will be better understood by reference to the Tables, in which:

Table 1 lists the commonly occurring amino acids together with their one letter and three letter abbreviations, and common protecting groups.

Table 2 shows DP178 carboxy truncations.

10 Table 3 shows DP178 amino truncations.

Table 4 shows DP107 carboxy truncations.

Table 5 shows DP107 amino truncations.

Table 6 shows HIV-2_{NH2} DP178 analog carboxy truncations.

Table 7 shows HIV-2_{NH2} DP178 analog amino truncations.

15 Table 8 shows RSV F2 region DP107 analog carboxy truncations.

Table 9 shows RSV F2 region DP107 analog amino truncations.

Table 10 shows RSV F1 region DP178 analog carboxy truncations.

Table 11 shows RSV F1 region DP178 analog amino truncations.

Table 12 shows HPV3 F1 region DP 178 analog carboxy truncations.

20 Table 13 shows HPV3 F1 region DP 178 analog amino truncations.

Table 14 shows HPV3 F1 region DP107 analog carboxy truncations.

Table 15 shows HPV3 F1 region DP107 analog amino truncations.

Table 16 shows representative anti-RSV peptides.

Table 17 shows representative anti-HPV3 peptides.

25 Table 18 shows representative anti-SIV peptides.

Table 19 shows representative anti-MeV peptides.

BRIEF DESCRIPTION OF SEQUENCE LISTING

30 The invention will be better understood by reference to the Sequence Listing, in which:

SEQ ID NO:1 shows the peptide sequence of DP178.

SEQ ID NO:2 shows the peptide sequence of DP107

SEQ ID NO:3-9 show peptide sequences of certain DP178 analogs.

5 SEQ ID NO:10-30 show the peptide sequences of RSV F1 region and F2 region corresponding to DP178 and DP107, and representative anti-RSV peptides;

SEQ ID NO:31-62 show the peptide sequences of HPIV3 F1 region corresponding to DP178 and DP107, and representative anti-HPIV3 peptides;

10 SEQ ID NO:63-73 show peptide sequences of SIV corresponding to DP178 and representative anti-SIV peptides; and

SEQ ID NO:74-78 show peptide sequences of MeV corresponding to DP178 and representative anti-MeV peptides.

DETAILED DESCRIPTION OF THE INVENTION

15 To ensure a complete understanding of the invention the following definitions are provided:

20 **Anti-viral peptides:** As used herein, anti-viral peptides shall refer to peptides that inhibit viral infection of cells, by, for example, inhibiting cell-cell fusion or free virus infection. The route of infection may involve membrane fusion, as occurs in the case of enveloped viruses, or some other fusion event involving viral and cellular structures. Peptides that inhibit viral infection by a particular virus may be referenced with respect to that particular virus, e.g., anti-HIV peptide, anti-RSV peptide, etc.

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Antifusogenic peptides: Antifusogenic peptides are peptides demonstrating an ability to inhibit or reduce the level of membrane fusion events between two or more entities, e.g., virus-cell or cell-cell, relative to the level of membrane fusion that occurs in the absence of the peptide.

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HIV and anti-HIV peptides: The human immunodeficiency virus (HIV), which is responsible for acquired immune deficiency syndrome (AIDS), is a member of the lentivirus family of retroviruses. There are two prevalent types of HIV, HIV-1 and HIV-2, with various strain of each having been identified. HIV targets CD-4+ cells, and viral entry depends on binding of the HIV protein gp41 to CD-4+ cell surface receptors. Anti-HIV peptides refer to peptides that exhibit anti-viral activity against HIV, including inhibiting CD-4+ cell infection by free virus and/or inhibiting HIV-induced syncytia formation between infected and uninfected CD-4+ cells.

SIV and anti-SIV peptides: Simian immunodeficiency viruses (SIV) are lentiviruses that cause acquired immunodeficiency syndrome (AIDS)-like illnesses in susceptible monkeys. Anti-SIV peptides are peptides that exhibit anti-viral activity against SIV, including inhibiting of infection of cells by the SIV virus and inhibiting syncytia formation between infected and uninfected cells.

RSV and anti-RSV peptides: Respiratory syncytial virus (RSV) is a respiratory pathogen, especially dangerous in infants and small children where it can cause bronchiolitis (inflammation of the small air passages) and pneumonia. RSVs are negative sense, single stranded RNA viruses and are members of the *Paramyxoviridae* family of viruses. The route of infection of RSV is typically through the mucous membranes by the respiratory tract, i.e., nose, throat, windpipe and bronchi and bronchioles. Anti-RSV peptides are peptides that exhibit anti-viral activity against RSV, including inhibiting mucous membrane cell infection by free RSV virus and syncytia formation between infection and uninfected cells.

HPV and anti-HPV peptides: Human parainfluenza virus (HPIV or HPV), like RSV, is another leading cause of respiratory tract disease, and like RSVs, are negative sense, single stranded RNA viruses that are members of the *Paramyxoviridae* family of viruses. There are four recognized serotypes of

HPIV -- HPIV-1, HPIV-2, HPIV-3 and HPIV-4. HPIV-1 is the leading cause of croup in children, and both HPIV-1 and HPIV-2 cause upper and lower respiratory tract illnesses. HPIV-3 is more often associated with bronchiolitis and pneumonia.

Anti-HPV peptides are peptides that exhibit anti-viral activity against HPV, including inhibiting infection by free HPV virus and syncytia formation between infected and uninfected cells.

MeV and anti-Mev peptides: Measles virus (VM or MeV) is an enveloped negative, single-stranded RNA virus belonging to the *Paramyxoviridae* family of viruses. Like RSV and HPV, MeV causes respiratory disease, and also produces an immuno-suppression responsible for additional, opportunistic infections. In some cases, MeV can establish infection of the brain leading to severe neurological complications. Anti-MeV peptides are peptides that exhibit anti-viral activity against MeV, including inhibiting infection by free MeV virus and syncytia formation between infected and uninfected cells.

DP-178 and DP178 analogs: Unless otherwise indicated explicitly or by context, DP-178 means the 36 amino acid DP-178 peptide corresponding to amino acid residues 638-673 of the gp41 glycoprotein of HIV-1 isolate LAI (HIV_{LAI}) and having the sequence:

YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF (SEQ ID NO:1)

as well as truncations, deletions and/or insertions thereof. Truncations of the DP178 peptide may comprise peptides of between 3-36 amino acids. Deletions consist of the removal of one or more amino acid residues from the DP178 peptide, and may involve the removal of a single contiguous portion of the peptide sequence or multiple portions. Insertions may comprise single amino acid residues or stretches of residues and may be made at the carboxy or amino terminal end of the DP178 peptide or at a position internal to the peptide.

DP178 peptide analogs are peptides whose amino acid sequences are comprised of the amino acid sequences of peptide regions of viruses other than HIV-1_{LAI} that correspond to the gp41 region from which DP178 was derived, as well as an truncations, deletions or insertions thereof. Such other viruses may include, but are not limited to, other HIV isolates such as HIV-2_{NH2}, respiratory syncytial virus (RSV), human parainfluenza virus (HPV), simian immunodeficiency virus (SIV), and measles virus (MeV). DP178 analogs also refer to those peptide sequences identified or recognized by the ALLMOT15, 107x178x4 and PLZIP search motifs described in U.S. Patent Nos. 6,013,263, 6,017,536 and 6,020,459 and incorporated herein, having structural and/or amino acid motif similarity to DP178. DP178 analogs further refer to peptides described as "DP178-like" as that term is defined in U.S. Patent Nos. 6,013,263, 6,017,536 and 6,020,459.

DP-107 and DP107 analogs: Unless otherwise indicated explicitly or by context, DP-107 means the 38 amino acid DP-107 peptide corresponding to amino acid residues 558-595 of the gp41 protein of HIV-1 isolate LAI (HIV_{LAI}) and having the sequence:

NNLLRAIEAQHLLQLTVWQIKQLQARILAVERYLKDQ (SEQ ID NO:2)

as well as truncations, deletions and/or insertions thereof. Truncations of the DP107 peptide may comprise peptides of between 3-38 amino acids. Deletions consist of the removal of one or more amino acid residues from the DP107 peptide, and may involve the removal of a single contiguous portion of the peptide sequence or multiple portions. Insertions may comprise single amino acid residues or stretches of residues and may be made at the carboxy or amino terminal end of the DP107 peptide or at a position internal to the peptide.

DP107 peptide analogs are peptides whose amino acid sequences are comprised of the amino acid sequences of peptide regions of viruses other than HIV-1_{LA1} that correspond to the gp41 region from which DP107 was derived, as well as truncations, deletions and/or insertions thereof. Such other viruses may include, but are not limited to, other HIV isolates such as HIV-2_{NH2}, respiratory syncytial virus (RSV), human parainfluenza virus (HPV), simian immunodeficiency virus (SIV), and measles virus (MeV). DP107 analogs also refer to those peptide sequences identified or recognized by the ALLMOTIS, 107x178x4 and PLZIP search motifs described in U.S. Patent Nos. 6,013,263, 6,017,536 and 6,020,459 and incorporated herein, having structural and/or amino acid motif similarity to DP107. DP107 analogs further refer to peptides described as "DP107-like" as that term is defined in U.S. Patent Nos. 6,013,263, 6,017,536 and 6,020,459.

Reactive Groups: Reactive groups are chemical groups capable of forming a covalent bond. Such reactive groups are coupled or bonded to a DP-107 or DP-178 peptide or analogs thereof or other anti-viral or anti-fusogenic peptide of interest. Reactive groups will generally be stable in an aqueous environment and will usually be carboxy, phosphoryl, or convenient acyl group, either as an ester or a mixed anhydride, or an imidate, thereby capable of forming a covalent bond with functionalities such as an amino group, a hydroxy or a thiol at the target site on mobile blood components. For the most part, the esters will involve phenolic compounds, or be thiol esters, alkyl esters, phosphate esters, or the like.

Functionalities: Functionalities are groups on blood components to which reactive groups on modified anti-viral peptides react to form covalent bonds. Functionalities include hydroxyl groups for bonding to ester reactive entities; thiol groups for bonding to maleimides, imidates and thioester groups; amino groups for bonding to carboxy, phosphoryl or acyl groups and carboxyl groups for bonding to amino groups.

Blood Components: Blood components may be either fixed or mobile.

Fixed blood components are non-mobile blood components and include tissues, membrane receptors, interstitial proteins, fibrin proteins, collagens, platelets, endothelial cells, epithelial cells and their associated membrane and membranous receptors, somatic body cells, skeletal and smooth muscle cells, neuronal components, osteocytes and osteoclasts and all body tissues especially those associated with the circulatory and lymphatic systems. Mobile blood components are blood components that do not have a fixed situs for any extended period of time, generally not exceeding 5, more usually one minute. These blood components are not membrane-associated and are present in the blood for extended periods of time and are present in a minimum concentration of at least 0.1 µg/ml. Mobile blood components include serum albumin, transferrin, ferritin and immunoglobulins such as IgM and IgG. The half-life of mobile blood components is at least about 12 hours.

Protective Groups: Protective groups are chemical moieties utilized to protect peptide derivatives from reacting with themselves. Various protective groups are disclosed herein and in U.S. 5,493,007, which is hereby incorporated by reference. Such protective groups include acetyl, fluorenylmethyloxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), benzyloxycarbonyl (CBZ), and the like. The specific protected amino acids are depicted in Table 1.

TABLE 1			
NATURAL AMINO ACIDS AND THEIR ABBREVIATIONS			
Name	3-Letter Abbreviation	1-Letter Abbreviation	Modified Amino Acids
Alanine	Ala	A	Fmoc-Ala-OH
Arginine	Arg	R	Fmoc-Arg(Pbf)-OH
Asparagine	Asn	N	Fmoc-Asn(Trt)-OH
Aspartic acid	Asp	D	Asp(tBu)-OH
Cysteine	Cys	C	Fmoc-Cys(Trt)
Glutamic acid	Glu	E	Fmoc-Glu(tBu)-OH
Glutamine	Gln	Q	Fmoc-Gln(Trt)-OH
Glycine	Gly	G	Fmoc-Gly-OH
Histidine	His	H	Fmoc-His(Trt)-OH
Isoleucine	Ile	I	Fmoc-Ile-OH
Leucine	Leu	L	Fmoc-Leu-OH
Lysine	Lys	Z	Boc-Lys(Aloc)-OH
Lysine	Lys	X	Fmoc-Lys(Aloc)-OH
Lysine	Lys	K	Fmoc-Lys(Mtt)-OH
Methionine	Met	M	Fmoc-Met-OH
Phenylalanine	Phe	F	Fmoc-Phe-OH
Proline	Pro	P	Fmoc-Pro-OH
Serine	Ser	S	Fmoc-Ser(tBu)-OH
Threonine	Thr	T	Fmoc-Thr(tBu)-OH
Tryptophan	Trp	W	Fmoc-Trp(Boc)-OH
Tyrosine	Tyr	Y	Boc-Tyr(tBu)-OH
Valine	Val	V	Fmoc-Val-OH

- Linking Groups:** Linking (spacer) groups are chemical moieties that link or connect reactive entities to antiviral or antifusogenic peptides. Linking groups may comprise one or more alkyl moieties, alkoxy moiety, alkenyl moiety, alkynyl moiety or amino moiety substituted by alkyl moieties, cycloalkyl moiety, polycyclic moiety, aryl moiety, polyaryl moieties, substituted aryl moieties, heterocyclic moieties, and substituted heterocyclic moieties. Linking groups may also comprise poly ethoxy amino acids, such as AEA ((2-amino) ethoxy acetic acid) or a preferred linking group AEEA ([2-(2-amino) ethoxy]] ethoxy acetic acid.

Sensitive Functional Groups – A sensitive functional group is a group of atoms that represents a potential reaction site on an antiviral and/or antifusogenic peptide. If present, a sensitive functional group may be chosen as the attachment point for the linker-reactive group modification. Sensitive functional groups
5 include but are not limited to carboxyl, amino, thiol, and hydroxyl groups.

Modified Peptides – A modified peptide is an antiviral and/or antifusogenic peptide that has been modified by attaching a reactive group. The reactive group may be attached to the peptide either via a linking group, or
10 optionally without using a linking group. It is also contemplated that one or more additional amino acids may be added to the peptide to facilitate the attachment of the reactive entity. Modified peptides may be administered *in vivo* such that conjugation with blood components occurs *in vivo*, or they may be first conjugated to blood components *in vitro* and the resulting conjugated peptide (as defined
15 below) administered *in vivo*.

Conjugated Peptides – A conjugated peptide is a modified peptide that has been conjugated to a blood component via a covalent bond formed between the reactive group of the modified peptide and the functionalities of the blood
20 component, with or without a linking group. As used throughout this application, the term “conjugated peptide” can be made more specific to refer to particular conjugated peptides, for example “conjugated DP178” or “conjugated DP107.”

Taking into account these definitions, the present invention takes advantage
25 of the properties of existing anti-viral and antifusogenic peptides. The viruses that may be inhibited by the peptides include, but are not limited to all strains of viruses listed, e.g., in U.S. Patent Nos. 6,013,263, 6,017,536 and 6,020,459 at Tables V-VII and IX-XIV therein. These viruses include, e.g., human retroviruses, including HIV-1, HIV-2, and human T-lymphocyte viruses (HTLV-I and HTLV-II),
30 and non-human retroviruses, including bovine leukosis virus, feline sarcoma virus,

feline leukemia virus, simian immunodeficiency virus (SIV), simian sarcoma virus, simian leukemia, and sheep progress pneumonia virus. Non-retroviral viruses may also be inhibited by the peptides of the present invention, including human respiratory syncytial virus (RSV), canine distemper virus, Newcastle
5 Disease virus, human parainfluenza virus (HPIV), influenza viruses, measles viruses (MeV), Epstein-Barr viruses, hepatitis B viruses, and simian Mason-Pfizer viruses. Non-enveloped viruses may also be inhibited by the peptides of the present invention, and include, but are not limited to, picornaviruses such as polio viruses, hepatitis A virus, enteroviruses, echoviruses, coxsackie viruses,
10 papovaviruses such as papilloma virus, parvoviruses, adenoviruses, and reoviruses.

As an example, the mechanism of action of HIV fusion peptides has been described as discussed in the background section of this application and antiviral and antifusogenic properties of the peptides have been well established. A synthetic peptide corresponding to the carboxyl-terminal ectodomain sequence (for
15 instance, amino acid residues 643-678 of HIV-1 class B, of the LAI strain or residues 638-673 from similar strain as well as residues 558-595) has been shown to inhibit virus-mediated cell-cell fusion completely at low concentration. The fusion peptide competes with the leucine zipper region of the native viral gp41 thus resulting in the interference of the fusion/infection of the virus into the cell.

20 The focus of the present invention is to modify a selected anti-viral and/or antifusogenic peptide with the DAC (Drug Activity Complex) technology to confer to this peptide improved bio-availability, extended half-life and better distribution through selective conjugation of the peptide onto a protein carrier but without modifying the peptide's anti-viral properties. The carrier of choice (but not
25 limited to) for this invention would be albumin conjugated through its free thiol by an anti-viral and/or antifusogenic peptide modified with a maleimide moiety.

Several peptide sequences have been described in the literature as highly potent for the prevention of HIV-1 fusion/infection. As examples, peptide DP178 binds to a conformation of gp41 that is relevant for fusion. Thus in one
30 embodiment of the invention, DP178 and DP178-like peptides are modified.

Likewise, other embodiments of the invention include modification of DP107 and DP107-like peptide for use against HIV, as well as peptides analagous to DP107 and DP178 that are found in RSV, HPV, MeV and SIV viruses.

5 1. **DP178 and DP107**

A. DP178 Peptides

 The DP178 peptide corresponds to amino acid residues 638 to 673 of the transmembrane protein gp41 from the HIV-1_{LA1} isolate, and has the 36 amino acid
10 sequence (reading from amino to carboxy terminus):

 NH₂-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-COOH (SEQ
 ID NO:1)

15 In addition to the full-length DP178 36-mer, the peptides of this invention include truncations of the DP178 peptide comprising peptides of between 3 and 36 amino acid residues (i.e., peptides ranging in size from a tripeptide to a 36-mer polypeptide), These truncated peptides are shown in Tables 2 and 3.

20 In addition amino acid substitutions of the DP178 peptide are also within the scope of the invention. HIV-1 and HIV-2 enveloped proteins are structurally distinct, but there exists a striking amino acid conservation within the DP178-corresponding regions of HIV-1 and HIV-2. The amino acid conservation is of a periodic nature, suggesting some conservation of structure and/or function.

25 Therefore, one possible class of amino acid substitutions would include those amino acid changes which are predicted to stabilize the structure of the DP178 peptides of the invention. Utilizing the DP178 and DP178 analog sequences described herein, the skilled artisan can readily compile DP178 consensus sequences and ascertain from these, conserved amino acid residues which would
30 represent preferred amino acid substitutions.

The amino acid substitutions may be of a conserved or non-conserved nature. Conserved amino acid substitutions consist of replacing one or more amino acids of the DP178 peptide sequence with amino acids of similar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to aspartic acid (D) amino acid substitution. Non-conserved substitutions consist of replacing one or more amino acids of the DP178 peptide sequence with amino acids possessing dissimilar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to valine (V) substitution.

Amino acid insertions of DP178 may consist of single amino acid residues or stretches of residues. The insertions may be made at the carboxy or amino terminal end of the DP178 or DP178 truncated peptides, as well as at a position internal to the peptide.

Such insertions will generally range from 2 to 15 amino acids in length. It is contemplated that insertions made at either the carboxy or amino terminus of the peptide of interest may be of a broader size range, with about 2 to about 50 amino acids being preferred. One or more such insertions may be introduced into DP178 or DP178 truncations, as long as such insertions result in peptides which may still be recognized by the 107x178x4, ALLMOT15 or PLZIP search motifs described above.

Preferred amino or carboxy terminal insertions are peptides ranging from about 2 to about 50 amino acid residues in length, corresponding to gp41 protein regions either amino to or carboxy to the actual DP178 gp41 amino acid sequence, respectively. Thus, a preferred amino terminal or carboxy terminal amino acid insertion would contain gp41 amino acid sequences found immediately amino to or carboxy to the DP178 region of the gp41 protein.

Deletions of DP178 or DP178 truncations are also within the scope of this invention. Such deletions consist of the removal of one or more amino acids from the DP178 or DP178-like peptide sequence, with the lower limit length of the resulting peptide sequence being 4 to 6 amino acids.

Such deletions may involve a single contiguous or greater than one discrete portion of the peptide sequences. One or more such deletions may be introduced into DP178 or DP178 truncations, as long as such deletions result in peptides which may still be recognized by the 107x178x4, ALLMOT15 or PLZIP search motifs described above.

B. DP107 Peptides

DP107 is a 38 amino acid peptide which exhibits potent antiviral activity, and corresponds to residues 558 to 595 of HIV-1_{LAI} isolate transmembrane (TM) gp41 glycoprotein, as shown here:

NH₂-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVEERYLKDQ-COOH
(SEQ ID NO:2)

In addition to the full-length DP107 38-mer, the DP107 peptides include truncations of the DP107 peptide comprising peptides of between 3 and 38 amino acid residues (i.e., peptides ranging in size from a tripeptide to a 38-mer polypeptide). These peptides are shown in Tables 4 and 5, below.

In addition, amino acid substitutions of the DP178 peptide are also within the scope of the invention. As for DP178, there also exists a striking amino acid conservation within the DP107-corresponding regions of HIV-1 and HIV-2, again of a periodic nature, suggesting conservation of structure and/or function. Therefore, one possible class of amino acid substitutions includes those amino acid

changes predicted to stabilize the structure of the DP107 peptides of the invention. Utilizing the DP107 and DP107 analog sequences described herein, the skilled artisan can readily compile DP107 consensus sequences and ascertain from these, conserved amino acid residues which would represent preferred amino acid substitutions.

The amino acid substitutions may be of a conserved or non-conserved nature. Conserved amino acid substitutions consist of replacing one or more amino acids of the DP107 peptide sequence with amino acids of similar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to aspartic acid (D) amino acid substitution. Non-conserved substitutions consist of replacing one or more amino acids of the DP107 peptide sequence with amino acids possessing dissimilar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to valine (V) substitution.

Amino acid insertions may consist of single amino acid residues or stretches of residues. The insertions may be made at the carboxy or amino terminal end of the DP107 or DP107 truncated peptides, as well as at a position internal to the peptide.

Such insertions will generally range from 2 to 15 amino acids in length. It is contemplated that insertions made at either the carboxy or amino terminus of the peptide of interest may be of a broader size range, with about 2 to about 50 amino acids being preferred. One or more such insertions may be introduced into DP107 or DP107 truncations, as long as such insertions result in peptides which may still be recognized by the 107x178x4, ALLMOT15 or PLZIP search motifs described above.

Preferred amino or carboxy terminal insertions are peptides ranging from about 2 to about 50 amino acid residues in length, corresponding to gp41 protein

regions either amino to or carboxy to the actual DP107 gp41 amino acid sequence, respectively. Thus, a preferred amino terminal or carboxy terminal amino acid insertion would contain gp41 amino acid sequences found immediately amino to or carboxy to the DP107 region of the gp41 protein.

5

Deletions of DP107 or DP107 truncations are also within the scope of this invention. Such deletions consist of the removal of one or more amino acids from the DP107 or DP107-like peptide sequence, with the lower limit length of the resulting peptide sequence being 4 to 6 amino acids.

10

Such deletions may involve a single contiguous or greater than one discrete portion of the peptide sequences. One or more such deletions may be introduced into DP107 or DP107 truncations, as long as such deletions result in peptides which may still be recognized by the 107x178x4, ALLMOT15 or PLZIP search motifs.

15

DP107 and DP107 truncations are more fully described in U.S. Patent No. 5,656,480, which is incorporated herein by reference in its entirety

20

2. DP107 and DP178 Analogs

25

Peptides corresponding to analogs of the DP178, DP178 truncations, DP107 and DP107 truncation sequences of the invention, described, above, may be found in other viruses, including, for example, non-HIV-1 enveloped viruses, non-enveloped viruses and other non-viral organisms.

30

Such DP178 and DP107 analogs may, for example, correspond to peptide sequences present in transmembrane ("TM") proteins of enveloped viruses and may, correspond to peptide sequences present in non enveloped and nonviral organisms. Such peptides may exhibit antifusogenic activity, antiviral activity, most particularly antiviral activity which is specific to the virus in which their

native sequences are found, or may exhibit an ability to modulate intracellular processes involving coiled-coil peptide structures.

A. DP178 analogs

5 DP178 analogs are peptides whose amino acid sequences are comprised of the amino acid sequences of peptide regions of, for example, other (i.e., other than HIV-1) viruses that correspond to the gp41 peptide region from which DP178 was derived. Such viruses may include, but are not limited to, other HIV-1 isolates and HIV-2 isolates.

10

DP178 analogs derived from the corresponding gp41 peptide region of other (i.e., non HIV-1LAI) HIV-1 isolates may include, for example, peptide sequences as shown below.

15 NH₂-YTNTIYTLLEESQNQQEKNEQEELLELDKWASLWNWF-COOH (SEQ ID NO:3)

NH₂-YTGIIYNLLEESQNQQEKNEQEELLELDKWANLWNWF-COOH (SEQ ID NO:4)

20 NH₂-YTSLIYSLLEKSQIQQEKNEQEELLELDKWASLWNWF-COOH (SEQ ID NO:5)

The peptides of SEQ ID NO:3, SEQ ID NO:4 and SEQ ID NO:5 are derived from HIV-1_{SF2}, HIV-1_{RF}, and HIV-1_{MN}, respectively. Other DP178 analogs include those derived from HIV-2, including the peptides of SEQ ID NO:6 and
25 SEQ ID NO:7, which are derived from HIV-2_{ROD} and HIV-2_{NIH2}, respectively. Still other useful analogs include the peptides of SEQ ID NO:8 and SEQ ID NO:9, which have been demonstrated to exhibit anti-viral activity.

In the present invention, it is preferred that the DP178 analogs represent
30 peptides whose amino acid sequences correspond to the DP178 region of the gp41

protein, it is also contemplated that the peptides disclosed herein may, additionally, include amino sequences, ranging from about 2 to about 50 amino acid residues in length, corresponding to gp41 protein regions either amino to or carboxy to the actual DP178 amino acid sequence.

5

Table 6 and Table 7 show some possible truncations of the HIV-2_{NH2} DP178 analog, which may comprise peptides of between 3 and 36 amino acid residues (i.e., peptides ranging in size from a tripeptide to a 36-mer polypeptide). Peptide sequences in these tables are listed from amino (left) to carboxy (right) terminus.

10

B. Additional DP178 Analogs and DP107 Analogs

DP178 and DP107 analogs are recognized or identified, for example, by utilizing one or more of the 107x178x4, ALLMOTIS or PLZIP computer-assisted search strategies described above. The search strategy identifies additional peptide regions which are predicted to have structural and/or amino acid sequence features similar to those of DP107 and/or DP178.

15

The search strategies are described fully in the example presented in Section 9 of US Patent Nos. 6,013,263, 6,017,536 and 6,020,459. While this search strategy is based, in part, on a primary amino acid motif deduced from DP107 and DP178, it is not based solely on searching for primary amino acid sequence homologies, as such protein sequence homologies exist within, but not between major groups of viruses. For example, primary amino acid sequence homology is high within the TM protein of different strains of HIV-1 or within the TM protein of different isolates of simian immunodeficiency virus (SIV).

20

25

The computer search strategy disclosed in US Patent Nos. 6,013,263, 6,017,536 and 6,020,459 successfully identified regions of proteins similar to

DP107 or DP178. This search strategy was designed to be used with a commercially-available sequence database package, preferably PC/Gene.

5 In US Patent Nos. 6,013,263, 6,017,536 and 6,020,459, a series of search motifs, the 107x178x4, ALLMOTIS and PLZIP motifs, were designed and engineered to range in stringency from strict to broad, with 107x178x4 being preferred. The sequences identified via such search motifs, such as those listed in Tables V-XIV, of US Patent Nos. 6,013,263, 6,017,536 and 6,020,459 and included in this application by incorporation by reference, potentially exhibit
10 antifusogenic, such as antiviral, activity, may additionally be useful in the identification of antifusogenic, such as antiviral, compounds.

3. Other Anti-Viral Peptides

A. Anti-RSV Peptides

15 Anti-RSV peptides include DP178 and/or DP107 analogs identified from corresponding peptide sequences in RSV which have further been identified to inhibit viral infection by RSV. Such peptides of interest include the peptides of Table 16 and peptides of SEQ ID NO:10 to SEQ ID NO:30. Of particular interest are the following peptides:

20

YTSVITIELSNIKENKCNGAKVKLIKQELDKYK (SEQ ID NO:14)
TSVITIELSNIKENKCNGAKVKLIKQELDKYKN (SEQ ID NO:15)
VITIELSNIKENKCNGAKVKLIKQELDKYKNAV (SEQ ID NO:16)

25

IALLSTNKAVVSLNGVSVLTSKVLDLKNYIDK (SEQ ID NO:29)

The peptide of SEQ ID NO:10 is derived from the F2 region of RSV and was identified in U.S. Patent Nos. 6,103,236 and 6,020,459 using the search motifs described as corresponding to DP107 and DP178 peptides (i.e., "DP107/178 like").

30

The peptides of SEQ ID NO:14 to SEQ ID NO:16 each have amino acid sequences contained within the peptide of SEQ ID NO:10 and each has been shown to exhibit anti-RSV activity, in particular, inhibiting fusion and syncytia

formation between RSV-infected and uninfected Hep-2 cells at concentrations of less than 50 µg/ml.

The peptide of SEQ ID NO:11 is derived from the F1 region of RSV and was identified in U.S. Patent Nos. 6,103,236 and 6,020,459 using the search motifs described as corresponding to DP107 (i.e., "DP107-like"). The peptide of SEQ ID NO:29 contains amino acid sequences contained within the peptide of SEQ ID NO:10 and likewise has been shown to exhibit anti-RSV activity, in particular, inhibiting fusion and syncytia formation between RSV-infected and uninfected Hep-2 cells at concentrations of less than 50 µg/ml.

15 **B. Anti-HPIV Peptides**

Anti-HPIV peptides include DP178 and/or DP107 analogs identified from corresponding peptide sequences in HPIV and which have further been identified to inhibit viral infection by HPIV. Such peptides of interest include the peptides of Table 17 and SEQ ID NO:31 to SEQ ID NO:62. Of particular interest are the following peptides:

	VEAQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI	(SEQ ID NO:52)
	RSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSV	(SEQ ID NO:58)
25	NSVALDPIDISIELNKA KSDLEESKEWIRRSNQKL	(SEQ ID NO:35)
	ALDPIDISIELNKA KSDLEESKEWIRRSNQKLDSI	(SEQ ID NO:38)
	LDPIDISIELNKA KSDLEESKEWIRRSNQKLDSIG	(SEQ ID NO:39)
	DPIDISIELNKA KSDLEESKEWIRRSNQKLDSIGN	(SEQ ID NO:40)
	PIDISIELNKA KSDLEESKEWIRRSNQKLDSIGNW	(SEQ ID NO:41)
30	IDISIELNKA KSDLEESKEWIRRSNQKLDSIGNWH	(SEQ ID NO:42)

The peptide of SEQ ID NO:31 is derived from the F1 region of HPIV-3 and was identified in U.S. Patent Nos. 6,103,236 and 6,020,459 using the search motifs described as corresponding to DP107 (i.e., "DP107-like"). The peptides of SEQ

5 ID NO:52 and SEQ ID NO:58 each have amino acid sequences contained within the peptide of SEQ ID NO:30 and each has been shown to exhibit anti-HPIV-3 activity, in particular, inhibiting fusion and syncytia formation between HPIV-3-infected Hep2 cells and uninfected CV-1W cells at concentrations of less than 1 $\mu\text{g/ml}$.

10 The peptide of SEQ ID NO:32 is also derived from the F1 region of HPIV-3 and was identified in U.S. Patent Nos. 6,103,236 and 6,020,459 using the search motifs described as corresponding to DP178 (i.e., "DP178-like"). The peptides of SEQ ID NO:35 and SEQ ID NO:38 to SEQ ID NO:42 each have amino acid sequences contained within the peptide of SEQ ID NO:32 and each also has been shown to exhibit anti-HPIV-3 activity, in particular, inhibiting fusion and syncytia formation between HPIV-3-infected Hep2 cells and uninfected CV-1W cells at concentrations of less than 1 $\mu\text{g/ml}$.

15

C. Anti-MeV Peptides

20 Anti-MeV peptides are DP178 and/or DP107 analogs identified from corresponding peptide sequences in measles virus (MeV) which have further been identified to inhibit viral infection by the measles virus. Such peptides of particular interest include the peptides of Table 19 and peptides of SEQ ID NO:74 to SEQ ID NO:86. Of particular interest are the peptides listed below.

25

HRIDLGPPISLERLDVGTNLGNIAIAKLEAKELLE (SEQ ID NO:77)
IDLGPPISLERLDVGTNLGNIAIAKLEAKELLE (SEQ ID NO:79)
LGPPISLERLDVGTNLGNIAIAKLEAKELLESDQ (SEQ ID NO:81)
PISLERLDVGTNLGNIAIAKLEAKELLESDQILR (SEQ ID NO:84)

30

Sequences derived from measles virus were identified in U.S. Patent Nos. 6,103,236 and 6,020,459 using the search motifs described as corresponding to

DP178 (i.e., "DP178-like"). The peptides of SEQ ID NO:77, SEQ ID NO:79, SEQ ID NO:81 and SEQ ID NO:83 each have amino acid sequences so identified, and each has been shown to exhibit anti-MeV activity, in particular, inhibiting fusion and syncytia formation between MeV-infected Hep2 and uninfected Vero cells at concentrations of less than 1 µg/ml.

D. Anti-SIV Peptides

Anti-SIV peptides are DP178 and/or DP107 analogs identified from corresponding peptide sequences in SIV which have further been identified to inhibit viral infection by SIV. Such peptides of interest include the peptides of Table 18 and peptides of SEQ ID NO:63 to SEQ ID NO:73. Of particular interest are the following peptides:

15	WQEWKVD FLEENITALLEEAQIQQEK NMYELQK (SEQ ID NO:64)
	QEWKVD FLEENITALLEEAQIQQEK NMYELQKL (SEQ ID NO:65)
	EWKVD FLEENITALLEEAQIQQEK NMYELQKLN (SEQ ID NO:66)
	WKVD FLEENITALLEEAQIQQEK NMYELQKLNS (SEQ ID NO:67)
	ERKVD FLEENITALLEEAQIQQEK NMYELQKLNSW (SEQ ID NO:68)
	RKVD FLEENITALLEEAQIQQEK NMYELQKLNSWD (SEQ ID NO:69)
20	KVD FLEENITALLEEAQIQQEK NMYELQKLNSWDV (SEQ ID NO:70)
	VD FLEENITALLEEAQIQQEK NMYELQKLNSWDVF (SEQ ID NO:71)
	DFLEENITALLEEAQIQQEK NMYELQKLNSWDVFG (SEQ ID NO:72)
	FLEENITALLEEAQIQQEK NMYELQKLNSWDVFGN (SEQ ID NO:73)

Sequences derived from SIV transmembrane fusion protein were identified in U.S. Patent Nos. 6,103,236 and 6,020,459 using the search motifs described as corresponding to DP178 (i.e., "DP178-like"). The peptides of SEQ ID NO:64 to SEQ ID NO:73 each have amino acid sequences so identified, and each has been shown to exhibit potent anti-SIV activity as crude peptides.

30

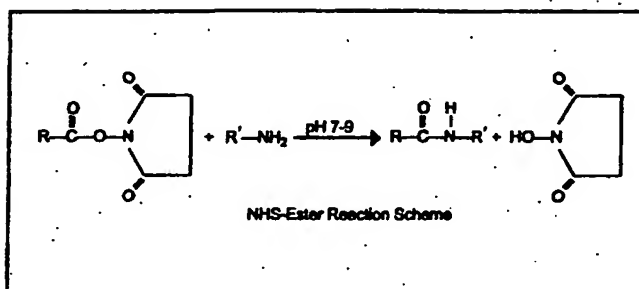
4. Modification of Anti-Viral and Antifusogenic Peptides

The invention contemplates modifying peptides that exhibit anti-viral and/or antifusogenic activity, including such modifications of DP-107 and DP-178 and analogs thereof. Such modified peptides can react with the available reactive

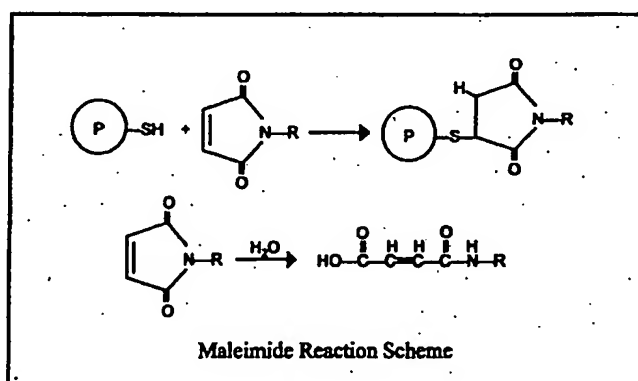
functionalities on blood components via covalent linkages. The invention also relates to such modifications, such combinations with blood components, and methods for their use. These methods include extending the effective therapeutic life of the conjugated anti-viral peptides derivatives as compared to administration of the unconjugated peptides to a patient. The modified peptides are of a type designated as a DAC (Drug Affinity Complex) which comprises the anti-viral peptide molecule and a linking group together with a chemically reactive group capable of reaction with a reactive functionality of a mobile blood protein. By reaction with the blood component or protein the modified peptide, or DAC, may be delivered via the blood to appropriate sites or receptors.

To form covalent bonds with functionalities on the protein, one may use as a reactive group a wide variety of active carboxyl groups, particularly esters, where the hydroxyl moiety is physiologically acceptable at the levels required to modify the peptide. While a number of different hydroxyl groups may be employed in these reactive groups, the most convenient would be N-hydroxysuccinimide or (NHS), N-hydroxy-sulfosuccinimide (sulfo-NHS). In preferred embodiments of this invention, the functionality on the protein will be a thiol group and the reactive group will be a maleimido-containing group such as gamma-maleimide-butyralamide (GMBA) or maleimidopropionic acid (MPA)

Primary amines are the principal targets for NHS esters. Accessible α -amine groups present on the N-termini of proteins react with NHS esters. However, α -amino groups on a protein may not be desirable or available for the NHS coupling. While five amino acids have nitrogen in their side chains, only the ϵ -amine of lysine reacts significantly with NHS esters. An amide bond is formed when the NHS ester conjugation reaction reacts with primary amines releasing N-hydroxysuccinimide as demonstrated in the schematic below.



In the preferred embodiments of this invention, the functional group on this protein will be a thiol group and the chemically reactive group will be a maleimido-containing group such as MPA or GMBA (gamma-maleimide-
 5 butyralamide). The maleimido group is most selective for sulfhydryl groups on peptides when the pH of the reaction mixture is kept between 6.5 and 7.4. At pH 7.0, the rate of reaction of maleimido groups with sulfhydryls is 1000-fold faster than with amines. A stable thioether linkage between the maleimido group and the
 10 sulfhydryl is formed which cannot be cleaved under physiological conditions, as demonstrated in the following schematic.



A. Specific Labeling.

Preferably, the modified peptides of this invention are designed to specifically react with thiol groups on mobile blood proteins. Such reaction is
 15 preferably established by covalent bonding of the peptide modified with a

maleimide link (e.g. prepared from GMBS, MPA or other maleimides) to a thiol group on a mobile blood protein such as serum albumin or IgG.

Under certain circumstances, specific labeling with maleimides offers several advantages over non-specific labeling of mobile proteins with groups such as NHS and sulfo-NHS. Thiol groups are less abundant *in vivo* than amino groups. Therefore, the maleimide-modified peptides of this invention, i.e., maleimide peptides, will covalently bond to fewer proteins. For example, in albumin (the most abundant blood protein) there is only a single thiol group. Thus, peptide-maleimide-albumin conjugates will tend to comprise approximately a 1:1 molar ratio of peptide to albumin. In addition to albumin, IgG molecules (class II) also have free thiols. Since IgG molecules and serum albumin make up the majority of the soluble protein in blood they also make up the majority of the free thiol groups in blood that are available to covalently bond to maleimide-modified peptides.

Further, even among free thiol-containing blood proteins, including IgGs, specific labeling with maleimides leads to the preferential formation of peptide-maleimide-albumin conjugates, due to the unique characteristics of albumin itself. The single free thiol group of albumin, highly conserved among species, is located at amino acid residue 34 (Cys³⁴). It has been demonstrated recently that the Cys³⁴ of albumin has increased reactivity relative to free thiols on other free thiol-containing proteins. This is due in part to the very low pK value of 5.5 for the Cys³⁴ of albumin. This is much lower than typical pK values for cysteine residues in general, which are typically about 8. Due to this low pK, under normal physiological conditions Cys³⁴ of albumin is predominantly in the ionized form, which dramatically increases its reactivity. In addition to the low pK value of Cys³⁴, another factor which enhances the reactivity of Cys³⁴ is its location, which is in a crevice close to the surface of one loop of region V of albumin. This location makes Cys³⁴ very available to ligands of all kinds, and is an important factor in Cys³⁴'s biological role as free radical trap and free thiol scavenger. These properties make Cys³⁴ highly reactive with maleimide-peptides, and the reaction

rate acceleration can be as much as 1000-fold relative to rates of reaction of maleimide-peptides with other free-thiol containing proteins.

Another advantage of peptide-maleimide-albumin conjugates is the reproducibility associated with the 1:1 loading of peptide to albumin specifically at Cys³⁴. Other techniques, such as glutaraldehyde, DCC, EDC and other chemical activations of, e.g, free amines, lack this selectivity. For example, albumin contains 52 lysine residues, 25-30 of which are located on the surface of albumin and therefore accessible for conjugation. Activating these lysine residues, or alternatively modifying peptides to couple through these lysine residues, results in a heterogenous population of conjugates. Even if 1:1 molar ratios of peptide to albumin are employed, the yield will consist of multiple conjugation products, some containing 0, 1, 2 or more peptides per albumin, and each having peptides randomly coupled at any one or more of the 25-30 available lysine sites. Given the numerous possible combinations, characterization of the exact composition and nature of each conjugate batch becomes difficult, and batch-to-batch reproducibility is all but impossible, making such conjugates less desirable as a therapeutic. Additionally, while it would seem that conjugation through lysine residues of albumin would at least have the advantage of delivering more therapeutic agent per albumin molecule, studies have shown that a 1:1 ratio of therapeutic agent to albumin is preferred. In an article by Stehle, et al., "The Loading Rate Determines Tumor Targeting properties of Methotrexate-Albumin Conjugates in Rats," Anti-Cancer Drugs, Vol. 8, pp. 677-685 (1988), incorporated herein in its entirety, the authors report that a 1:1 ratio of the anti-cancer methotrexate to albumin conjugated via glutaraldehyde gave the most promising results. These conjugates were preferentially taken up by tumor cells, whereas conjugates bearing 5:1 to 20:1 methotrexate molecules had altered HPLC profiles and were quickly taken up by the liver *in vivo*. It is postulated that at these higher ratios, conformational changes to albumin diminish its effectiveness as a therapeutic carrier.

Through controlled administration of maleimide-peptides *in vivo*, one can control the specific labeling of albumin and IgG *in vivo*. In typical administrations, 80-90% of the administered maleimide-peptides will label albumin and less than 5% will label IgG. Trace labeling of free thiols such as glutathione will also occur. Such specific labeling is preferred for *in vivo* use as it permits an accurate calculation of the estimated half-life of the administered agent.

In addition to providing controlled specific *in vivo* labeling, maleimide-peptides can provide specific labeling of serum albumin and IgG *ex vivo*. Such *ex vivo* labeling involves the addition of maleimide-peptides to blood, serum or saline solution containing serum albumin and/or IgG. Once conjugation has occurred *ex vivo* with the maleimide-peptides, the blood, serum or saline solution can be readministered to the patient's blood for *in vivo* treatment.

In contrast to NHS-peptides, maleimide-peptides are generally quite stable in the presence of aqueous solutions and in the presence of free amines. Since maleimide-peptides will only react with free thiols, protective groups are generally not necessary to prevent the maleimide-peptides from reacting with itself. In addition, the increased stability of the modified peptide permits the use of further purification steps such as HPLC to prepare highly purified products suitable for *in vivo* use. Lastly, the increased chemical stability provides a product with a longer shelf life.

B. Non-Specific Labeling.

The anti-viral peptides of the invention may also be modified for non-specific labeling of blood components. Bonds to amino groups will also be employed, particularly with the formation of amide bonds for non-specific labeling. To form such bonds, one may use as a chemically reactive group a wide variety of active carboxyl groups, particularly esters, where the hydroxyl moiety is physiologically acceptable at the levels required. While a number of different hydroxyl groups may be employed in these linking agents, the most convenient would be N-hydroxysuccinimide (NHS) and N-hydroxy-sulfosuccinimide (sulfo-

NHS).

Other linking agents which may be utilized are described in U.S. Patent 5,612,034, which is hereby incorporated herein.

5 The various sites with which the chemically reactive group of the modified peptides may react *in vivo* include cells, particularly red blood cells (erythrocytes) and platelets, and proteins, such as immunoglobulins, including IgG and IgM, serum albumin, ferritin, steroid binding proteins, transferrin, thyroxin binding protein, α -2-macroglobulin, and the like. Those receptors with which the modified peptides react, which are not long-lived, will generally be eliminated
10 from the human host within about three days. The proteins indicated above (including the proteins of the cells) will remain at least three days, and may remain five days or more (usually not exceeding 60 days, more usually not exceeding 30 days) particularly as to the half life, based on the concentration in the blood.

15 For the most part, reaction will be with mobile components in the blood, particularly blood proteins and cells, more particularly blood proteins and erythrocytes. By "mobile" is intended that the component does not have a fixed situs for any extended period of time, generally not exceeding 5 minutes, more usually one minute, although some of the blood component may be relatively stationary for extended periods of time. Initially, there will be a relatively
20 heterogeneous population of functionalized proteins and cells. However, for the most part, the population within a few days will vary substantially from the initial population, depending upon the half-life of the functionalized proteins in the blood stream. Therefore, usually within about three days or more, IgG will become the predominant functionalized protein in the blood stream.

25 Usually, by day 5 post-administration, IgG, serum albumin and erythrocytes will be at least about 60 mole %, usually at least about 75 mole %, of the conjugated components in blood, with IgG, IgM (to a substantially lesser extent) and serum albumin being at least about 50 mole %, usually at least about 75 mole %, more usually at least about 80 mole %, of the non-cellular conjugated
30 components.

The desired conjugates of non-specific modified peptides to blood components may be prepared *in vivo* by administration of the modified peptides to the patient, which may be a human or other mammal. The administration may be done in the form of a bolus or introduced slowly over time by infusion using metered flow or the like.

If desired, the subject conjugates may also be prepared *ex vivo* by combining blood with modified peptides of the present invention, allowing covalent bonding of the modified peptides to reactive functionalities on blood components and then returning or administering the conjugated blood to the host.

Moreover, the above may also be accomplished by first purifying an individual blood component or limited number of components, such as red blood cells, immunoglobulins, serum albumin, or the like, and combining the component or components *ex vivo* with the chemically reactive modified peptides. The functionalized blood or blood component may then be returned to the host to provide *in vivo* the subject therapeutically effective conjugates. The blood also may be treated to prevent coagulation during handling *ex vivo*.

5. Synthesis of Modified Anti-Viral and Anti-Fusogenic Peptides

A. Peptide Synthesis

Anti-viral and/or anti-fusogenic peptides according to the present invention may be synthesized by standard methods of solid phase peptide chemistry known to those of ordinary skill in the art. For example, peptides may be synthesized by solid phase chemistry techniques following the procedures described by Steward and Young (Steward, J. M. and Young, J. D., Solid Phase Peptide Synthesis, 2nd Ed., Pierce Chemical Company, Rockford, Ill., (1984) using an Applied Biosystem synthesizer. Similarly, multiple peptide fragments may be synthesized then linked together to form larger peptides. These synthetic peptides can also be made with amino acid substitutions at specific locations.

For solid phase peptide synthesis, a summary of the many techniques may be found in J. M. Stewart and J. D. Young, Solid Phase Peptide Synthesis, W. H.

Freeman Co. (San Francisco), 1963 and J. Meienhofer, *Hormonal Proteins and Peptides*, vol. 2, p. 46, Academic Press (New York), 1973. For classical solution synthesis see G. Schroder and K. Lupke, *The Peptides*, Vol. 1, Academic Press (New York). In general, these methods comprise the sequential addition of one or
5 more amino acids or suitably protected amino acids to a growing peptide chain. Normally, either the amino or carboxyl group of the first amino acid is protected by a suitable protecting group. The protected or derivatized amino acid is then either attached to an inert solid support or utilized in solution by adding the next amino acid in the sequence having the complimentary (amino or carboxyl) group
10 suitably protected and under conditions suitable for forming the amide linkage. The protecting group is then removed from this newly added amino acid residue and the next amino acid (suitably protected) is added, and so forth.

After all the desired amino acids have been linked in the proper sequence, any remaining protecting groups (and any solid support) are removed sequentially
15 or concurrently to afford the final polypeptide. By simple modification of this general procedure, it is possible to add more than one amino acid at a time to a growing chain, for example, by coupling (under conditions which do not racemize chiral centers) a protected tripeptide with a properly protected dipeptide to form, after deprotection, a pentapeptide.

20 A particularly preferred method of preparing compounds of the present invention involves solid phase peptide synthesis wherein the amino acid α -N-terminal is protected by an acid or base sensitive group. Such protecting groups should have the properties of being stable to the conditions of peptide linkage formation while being readily removable without destruction of the growing
25 peptide chain or racemization of any of the chiral centers contained therein. Suitable protecting groups are 9-fluorenylmethyloxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), biphenylisopropylloxycarbonyl, t-amylloxycarbonyl, isobornylloxycarbonyl, α , α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, o-nitrophenylsulfenyl, 2-cyano-t-butyloxycarbonyl,
30 and the like. The 9-fluorenyl-methyloxycarbonyl (Fmoc) protecting group is

particularly preferred for the synthesis of the peptides of the present invention. Other preferred side chain protecting groups are, for side chain amino groups like lysine and arginine, 2,2,5,7,8-pentamethylchroman-6-sulfonyl (pmc), nitro, p-toluenesulfonyl, 4-methoxybenzene-sulfonyl, Cbz, Boc, and
5 adamantyloxycarbonyl; for tyrosine, benzyl, o-bromobenzyloxycarbonyl, 2,6-dichlorobenzyl, isopropyl, t-butyl (t-Bu), cyclohexyl, cyclophenyl and acetyl (Ac); for serine, t-butyl, benzyl and tetrahydropyranyl; for histidine, trityl, benzyl, Cbz, p-toluenesulfonyl and 2,4-dinitrophenyl; for tryptophan, formyl; for aspartic acid and glutamic acid, benzyl and t-butyl and for cysteine, triphenylmethyl (trityl).

10 In the solid phase peptide synthesis method, the α -C-terminal amino acid is attached to a suitable solid support or resin. Suitable solid supports useful for the above synthesis are those materials which are inert to the reagents and reaction conditions of the stepwise condensation-deprotection reactions, as well as being insoluble in the media used. The preferred solid support for synthesis of α -C-
15 terminal carboxy peptides is 4-hydroxymethylphenoxymethyl-copoly(styrene-1% divinylbenzene). The preferred solid support for α -C-terminal amide peptides is the 4-(2',4'-dimethoxyphenyl-Fmoc-aminomethyl)phenoxyacetamidoethyl resin available from Applied Biosystems (Foster City, Calif.). The α -C-terminal amino acid is coupled to the resin by means of N,N'-dicyclohexylcarbodiimide (DCC),
20 N,N'-diisopropylcarbodiimide (DIC) or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HBTU), with or without 4-dimethylaminopyridine (DMAP), 1-hydroxybenzotriazole (HOBT), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium-hexafluorophosphate (BOP) or bis(2-oxo-3-oxazolidinyl)phosphine chloride (BOPCl), mediated coupling for from
25 about 1 to about 24 hours at a temperature of between 10° and 50°C in a solvent such as dichloromethane or DMF.

When the solid support is 4-(2',4'-dimethoxyphenyl-Fmoc-aminomethyl)phenoxy-acetamidoethyl resin, the Fmoc group is cleaved with a secondary amine, preferably piperidine, prior to coupling with the α -C-terminal
30 amino acid as described above. The preferred method for coupling to the

deprotected 4-(2',4'-dimethoxyphenyl-Fmoc-aminomethyl)phenoxy-acetamidoethyl resin is O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluoro-phosphate (HBTU, 1 equiv.) and 1-hydroxybenzotriazole (HOBT, 1 equiv.) in DMF. The coupling of successive
5 protected amino acids can be carried out in an automatic polypeptide synthesizer as is well known in the art. In a preferred embodiment, the α -N-terminal amino acids of the growing peptide chain are protected with Fmoc. The removal of the Fmoc protecting group from the α -N-terminal side of the growing peptide is accomplished by treatment with a secondary amine, preferably piperidine. Each
10 protected amino acid is then introduced in about 3-fold molar excess, and the coupling is preferably carried out in DMF. The coupling agent is normally O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU, 1 equiv.) and 1-hydroxybenzotriazole (HOBT, 1 equiv.).

At the end of the solid phase synthesis, the polypeptide is removed from
15 the resin and deprotected, either in successively or in a single operation. Removal of the polypeptide and deprotection can be accomplished in a single operation by treating the resin-bound polypeptide with a cleavage reagent comprising thioanisole, water, ethanedithiol and trifluoroacetic acid. In cases wherein the α -C-terminal of the polypeptide is an alkylamide, the resin is cleaved by aminolysis
20 with an alkylamine. Alternatively, the peptide may be removed by transesterification, e.g. with methanol, followed by aminolysis or by direct transamidation. The protected peptide may be purified at this point or taken to the next step directly. The removal of the side chain protecting groups is accomplished using the cleavage cocktail described above. The fully deprotected peptide is
25 purified by a sequence of chromatographic steps employing any or all of the following types: ion exchange on a weakly basic resin (acetate form); hydrophobic adsorption chromatography on underivitized polystyrene-divinylbenzene (for example, Amberlite XAD); silica gel adsorption chromatography; ion exchange chromatography on carboxymethylcellulose; partition chromatography, e.g. on
30 Sephadex G-25, LH-20 or countercurrent distribution; high performance liquid

chromatography (HPLC), especially reverse-phase HPLC on octyl- or octadecylsilyl-silica bonded phase column packing.

Molecular weights of these ITPs are determined using Fast Atom Bombardment (FAB) Mass Spectroscopy.

5

(1) N-Terminal Protective Groups

As discussed above, the term "N-protecting group" refers to those groups intended to protect the α -N-terminal of an amino acid or peptide or to otherwise protect the amino group of an amino acid or peptide against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in
10 Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. Additionally, protecting groups can be used as pro-drugs which are readily cleaved *in vivo*, for example, by enzymatic hydrolysis, to release the biologically active parent. α -N-protecting
15 groups comprise loweralkanoyl groups such as formyl, acetyl ("Ac"), propionyl, pivaloyl, t-butylacetyl and the like; other acyl groups include 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like;
20 carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl,
25
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cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; arylalkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl, 9-fluorenylmethyloxycarbonyl (Fmoc) and the like and silyl groups such as trimethylsilyl and the like.

5

(2) Carboxy Protective Groups

As discussed above, the term "carboxy protecting group" refers to a carboxylic acid protecting ester or amide group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are performed. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated by reference. Additionally, a carboxy protecting group can be used as a pro-drug whereby the carboxy protecting group can be readily cleaved *in vivo*, for example by enzymatic hydrolysis, to release the biologically active parent.

Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields as described in U.S. Pat. Nos. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference. Representative carboxy protecting groups are C₁-C₈ loweralkyl (e.g., methyl, ethyl or t-butyl and the like); arylalkyl such as phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl such as phenylethenyl and the like; aryl and substituted derivatives thereof such as 5-indanyl and the like; dialkylaminoalkyl such as dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxy)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl such as benzoyloxymethyl, benzoyloxyethyl and the like;

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arylalkylcarbonyloxyalkyl such as benzylcarbonyloxymethyl, 2-
 benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl or
 cycloalkyloxycarbonylalkyl such as methoxycarbonylmethyl,
 cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl and the like;
 5 alkoxycarbonyloxyalkyl or cycloalkyloxycarbonyloxyalkyl such as
 methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-
 1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like;
 aryloxycarbonyloxyalkyl such as 2-(phenoxy carbonyloxy)ethyl, 2-(5-
 indanyloxycarbonyloxy)ethyl and the like; alkoxyalkylcarbonyloxyalkyl such as 2-
 10 (1-methoxy-2-methylpropan-2-oyloxy)ethyl and like;
 arylalkyloxycarbonyloxyalkyl such as 2-(benzyloxycarbonyloxy)ethyl and the like;
 arylalkenyloxycarbonyloxyalkyl such as 2-(3-phenylpropen-2-
 yloxycarbonyloxy)ethyl and the like; alkoxycarbonylaminoalkyl such as t-
 butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl such
 15 as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl such as
 acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl such as 4-
 methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl
 such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like;
 (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl such as (5-t-butyl-2-oxo-1,3-
 20 dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl
 such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

Representative amide carboxy protecting groups are aminocarbonyl and
 loweralkylaminocarbonyl groups.

25 Preferred carboxy-protected compounds of the invention are compounds
 wherein the protected carboxy group is a loweralkyl, cycloalkyl or arylalkyl ester,
 for example, methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-
 butyl ester, isobutyl ester, amyl ester, isoamyl ester, octyl ester, cyclohexyl ester,
 phenylethyl ester and the like or an alkanoyloxyalkyl, cycloalkanoyloxyalkyl,
 30 aroyloxyalkyl or an arylalkylcarbonyloxyalkyl ester. Preferred amide carboxy

protecting groups are loweralkylaminocarbonyl groups. For example, aspartic acid may be protected at the α -C-terminal by an acid labile group (e.g. t-butyl) and protected at the β -C-terminal by a hydrogenation labile group (e.g. benzyl) then deprotected selectively during synthesis.

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B. Peptide Modification

The manner of producing the modified peptides of the present invention will vary widely, depending upon the nature of the various elements comprising the peptide. The synthetic procedures will be selected so as to be simple, provide
10 for high yields, and allow for a highly purified stable product. Normally, the chemically reactive group will be created at the last stage of the synthesis, for example, with a carboxyl group, esterification to form an active ester. Specific methods for the production of modified peptides of the present invention are described below.

15 Specifically, the selected peptide is first assayed for anti-viral activity, and then is modified with the linking group only at either the N-terminus, C-terminus or interior of the peptide. The anti-viral activity of this modified peptide-linking group is then assayed. If the anti-viral activity is not reduced dramatically (i.e., reduced less than 10-fold), then the stability of the modified peptide-linking group
20 is measured by its *in vivo* lifetime. If the stability is not improved to a desired level, then the peptide is modified at an alternative site, and the procedure is repeated until a desired level of anti-viral and stability is achieved.

More specifically, each peptide selected to undergo modification with a linker and a reactive entity group will be modified according to the following
25 criteria: if a terminal carboxylic group is available on the peptide and is not critical for the retention of anti-viral activity, and no other sensitive functional group is present on the peptide, then the carboxylic acid will be chosen as attachment point for the linker-reactive group modification. If the terminal carboxylic group is involved in anti-viral activity, or if no carboxylic acids are available, then any
30 other sensitive functional group not critical for the retention of anti-viral activity

will be selected as the attachment point for the linker-reactive entity modification. If several sensitive functional groups are available on a peptide, a combination of protecting groups will be used in such a way that after addition of the linker/reactive entity and deprotection of all the protected sensitive functional groups, retention of anti-viral activity is still obtained. If no sensitive functional groups are available on the peptide, or if a simpler modification route is desired, synthetic efforts will allow for a modification of the original peptide in such a way that retention of anti-viral is maintained. In this case the modification will occur at the opposite end of the peptide

An NHS derivative may be synthesized from a carboxylic acid in absence of other sensitive functional groups in the peptide. Specifically, such a peptide is reacted with N-hydroxysuccinimide in anhydrous CH_2Cl_2 and EDC, and the product is purified by chromatography or recrystallized from the appropriate solvent system to give the NHS derivative.

Alternatively, an NHS derivative may be synthesized from a peptide that contains an amino and/or thiol group and a carboxylic acid. When a free amino or thiol group is present in the molecule, it is preferable to protect these sensitive functional groups prior to perform the addition of the NHS derivative. For instance, if the molecule contains a free amino group, a transformation of the amine into a Fmoc or preferably into a tBoc protected amine is necessary prior to perform the chemistry described above. The amine functionality will not be deprotected after preparation of the NHS derivative. Therefore this method applies only to a compound whose amine group is not required to be freed to induce the desired anti-viral effect. If the amino group needs to be freed to retain the original properties of the molecule, then another type of chemistry described below has to be performed.

In addition, an NHS derivative may be synthesized from a peptide containing an amino or a thiol group and no carboxylic acid. When the selected molecule contains no carboxylic acid, an array of bifunctional linkers can be used to convert the molecule into a reactive NHS derivative. For instance, ethylene

glycol-bis(succinimidyldisuccinate) (EGS) and triethylamine dissolved in DMF and added to the free amino containing molecule (with a ratio of 10:1 in favor of EGS) will produce the mono NHS derivative. To produce an NHS derivative from a thiol derivatized molecule, one can use N-[γ -maleimidobutyryloxy]succinimide ester (GMBS) and triethylamine in DMF. The maleimido group will react with the free thiol and the NHS derivative will be purified from the reaction mixture by chromatography on silica or by HPLC.

An NHS derivative may also be synthesized from a peptide containing multiple sensitive functional groups. Each case will have to be analyzed and solved in a different manner. However, thanks to the large array of protecting groups and bifunctional linkers that are commercially available, this invention is applicable to any peptide with preferably one chemical step only to modify the peptide (as described above) or two steps (as described above involving prior protection of a sensitive group) or three steps (protection, activation and deprotection). Under exceptional circumstances only, would multiple steps (beyond three steps) synthesis be required to transform a peptide into an active NHS or maleimide derivative.

A maleimide derivative may also be synthesized from a peptide containing a free amino group and a free carboxylic acid. To produce a maleimide derivative from a amino derivatized molecule, one can use N-[γ -maleimidobutyryloxy]succinimide ester (GMBS) and triethylamine in DMF. The succinimide ester group will react with the free amino and the maleimide derivative will be purified from the reaction mixture by crystallization or by chromatography on silica or by HPLC.

Finally, a maleimide derivative may be synthesized from a peptide containing multiple other sensitive functional groups and no free carboxylic acids. When the selected molecule contains no carboxylic acid, an array of bifunctional crosslinking reagents can be used to convert the molecule into a reactive NHS derivative. For instance maleimidopropionic acid (MPA) can be coupled to the free amine to produce a maleimide derivative through reaction of the free amine

with the carboxylic group of MPA using HBTU/HOBt/DIEA activation in DMF.

Many other commercially available heterobifunctional crosslinking reagents can alternatively be used when needed. A large number of bifunctional compounds are available for linking to entities. Illustrative reagents include:

5 azidobenzoyl hydrazide, N-[4-(p-azidosalicylamino)butyl]-3'-[2'-pyridyldithio)propionamide), bis-sulfosuccinimidyl suberate, dimethyl adipimidate, disuccinimidyl tartrate, N-y-maleimidobutyryloxysuccinimide ester, N-hydroxy sulfosuccinimidyl-4-azidobenzoate, N-succinimidyl [4-azidophenyl]-1,3'-dithiopropionate, N-succinimidyl [4-iodoacetyl]aminobenzoate,

10 glutaraldehyde, and succinimidyl 4-[N-maleimidomethyl]cyclohexane-1-carboxylate.

6. Uses of Modified Anti-Viral Peptides

Modified anti-viral peptides of the invention may be used as a therapeutic agent in the treatment of patients who are suffering from viral infection, and can be administered to patients according to the methods described below and other methods known in the art. Effective therapeutic dosages of the modified peptides may be determined through procedures well known by those in the art and will take into consideration any concerns over potential toxicity of the peptide.

20 The modified peptides can also be administered prophylactically to previously uninfected individuals. This can be advantageous in cases where an individual has been subjected to a high risk of exposure to a virus, as can occur when individual has been in contact with an infected individual where there is a high risk of viral transmission. This can be expecially advantageous where there is known cure for the virus, such as the HIV virus. As a example, prophylactic administration of a modified anti-HIV peptide would be advantageous in a situation where a health care worker has been exposed to blood from an HIV-infected individual, or in other situations where an individual engaged in high-risk activities that potentially expose that individual to the HIV virus.

7. Administration of Modified Anti-Viral and Anti-Fusogenic Peptides

Generally, the modified peptides will be administered in a physiologically acceptable medium, e.g. deionized water, phosphate buffered saline (PBS), saline, aqueous ethanol or other alcohol, plasma, proteinaceous solutions, mannitol, aqueous glucose, alcohol, vegetable oil, or the like. Other additives which may be included include buffers, where the media are generally buffered at a pH in the range of about 5 to 10, where the buffer will generally range in concentration from about 50 to 250 mM, salt, where the concentration of salt will generally range from about 5 to 500 mM, physiologically acceptable stabilizers, and the like. The compositions may be lyophilized for convenient storage and transport.

The subject modified peptides will for the most part be administered parenterally, such as intravenously (IV), intraarterially (IA), intramuscularly (IM), subcutaneously (SC), or the like. Administration may in appropriate situations be by transfusion. In some instances, where reaction of the functional group is relatively slow, administration may be oral, nasal, rectal, transdermal or aerosol, where the nature of the conjugate allows for transfer to the vascular system. Usually a single injection will be employed although more than one injection may be used, if desired. The modified peptides may be administered by any convenient means, including syringe, trocar, catheter, or the like.

The particular manner of administration will vary depending upon the amount to be administered, whether a single bolus or continuous administration, or the like. Preferably, the administration will be intravascularly, where the site of introduction is not critical to this invention, preferably at a site where there is rapid blood flow, e.g., intravenously, peripheral or central vein. Other routes may find use where the administration is coupled with slow release techniques or a protective matrix. The intent is that the modified peptide be effectively distributed in the blood, so as to be able to react with the blood components. The concentration of the conjugate will vary widely, generally ranging from about 1 pg/ml to 50 mg/ml. The total administered intravascularly will generally be in the range of about 0.1 mg/ml to about 10 mg/ml, more usually about 1 mg/ml to about

5 mg/ml.

By bonding to long-lived components of the blood, such as immunoglobulin, serum albumin, red blood cells and platelets, a number of advantages ensue. The activity of the peptide is extended for days to weeks. Only one administration need be given during this period of time. Greater specificity can be achieved, since the active compound will be primarily bound to large molecules, where it is less likely to be taken up intracellularly to interfere with other physiological processes.

8. **Monitoring the Presence of Modified Peptides**

The blood of the mammalian host may be monitored for the presence of the modified peptide compound one or more times. By taking a portion or sample of the blood of the host, one may determine whether the peptide has become bound to the long-lived blood components in sufficient amount to be therapeutically active and, thereafter, the level of the peptide compound in the blood. If desired, one may also determine to which of the blood components the peptide is bound. This is particularly important when using non-specific modified peptides. For specific maleimide-modified peptides, it is much simpler to calculate the half life of serum albumin and IgG.

A. **Immuno Assays**

Another aspect of this invention relates to methods for determining the concentration of the anti-viral peptides and/or analogs, or their derivatives and conjugates in biological samples (such as blood) using antibodies specific for the peptides, peptide analogs or their derivatives and conjugates, and to the use of such antibodies as a treatment for toxicity potentially associated with such peptides, analogs, and/or their derivatives or conjugates. This is advantageous because the increased stability and life of the peptides in vivo in the patient might lead to novel problems during treatment, including increased possibility for toxicity.

The use of anti-therapeutic agent antibodies, either monoclonal or

polyclonal, having specificity for a particular peptide, peptide analog or derivative thereof, can assist in mediating any such problem. The antibody may be generated or derived from a host immunized with the particular peptide, analog or derivative thereof, or with an immunogenic fragment of the agent, or a synthesized
5 immunogen corresponding to an antigenic determinant of the agent. Preferred antibodies will have high specificity and affinity for native, modified and conjugated forms of the peptide, peptide analog or derivative. Such antibodies can also be labeled with enzymes, fluorochromes, or radiolables.

Antibodies specific for modified peptides may be produced by using
10 purified peptides for the induction of peptide-specific antibodies. By induction of antibodies, it is intended not only the stimulation of an immune response by injection into animals, but analogous steps in the production of synthetic antibodies or other specific binding molecules such as screening of recombinant immunoglobulin libraries. Both monoclonal and polyclonal antibodies can be
15 produced by procedures well known in the art.

The anti-peptide antibodies may be used to treat toxicity induced by administration of the modified peptide, analog or derivative thereof, and may be used ex vivo or in vivo. Ex vivo methods would include immuno-dialysis treatment for toxicity employing anti-therapeutic agent antibodies fixed to solid
20 supports. In vivo methods include administration of anti-therapeutic agent antibodies in amounts effective to induce clearance of antibody-agent complexes.

The antibodies may be used to remove the modified peptides, analogs or derivatives thereof, and conjugates thereof, from a patient's blood ex vivo by contacting the blood with the antibodies under sterile conditions. For example, the
25 antibodies can be fixed or otherwise immobilized on a column matrix and the patient's blood can be removed from the patient and passed over the matrix. The modified peptide, peptide analogs, derivatives or conjugates will bind to the antibodies and the blood containing a low concentration of peptide, analog, derivative or conjugate, then may be returned to the patient's circulatory system.
30 The amount of peptide compound removed can be controlled by adjusting the

pressure and flow rate.

5 Preferential removal of the peptides, analogs, derivatives and conjugates from the plasma component of a patient's blood can be effected, for example, by the use of a semipermeable membrane, or by otherwise first separating the plasma component from the cellular component by ways known in the art prior to passing the plasma component over a matrix containing the anti-therapeutic antibodies. Alternatively the preferential removal of peptide-conjugated blood cells, including red blood cells, can be effected by collecting and concentrating the blood cells in the patient's blood and contacting those cells with fixed anti-therapeutic antibodies to the exclusion of the serum component of the patient's blood.

10 The anti-therapeutic antibodies can be administered in vivo, parenterally, to a patient that has received the peptide, analogs, derivatives or conjugates for treatment. The antibodies will bind peptide compounds and conjugates. Once bound the peptide activity will be hindered if not completely blocked thereby reducing the biologically effective concentration of peptide compound in the patient's bloodstream and minimizing harmful side effects. In addition, the bound antibody-peptide complex will facilitate clearance of the peptide compounds and conjugates from the patient's blood stream.

20 The invention having been fully described can be further appreciated and understood with reference to the following non-limiting examples.

Example 1**Preparation of a Modified DP 178 --Synthesis of
YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFK(MPA)-NH₂**

5 In this example, DP178 (SEQ ID NO:1) is synthesized and modified to include a linker and maleimide group according to the following synthesis scheme. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, DP178 is a potent inhibitor of HIV-1, and inhibits both cell-induced syncytia formation between HIV-1 infected and uninfected cells and infection of uninfected cells by cell-free HIV-1

10 virus.

 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The

15 following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Phe-OH, Fmoc-Trp(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Leu-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ala-OH, Fmoc-Trp(Boc)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Met-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH; Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Ser(tBu)-OH, Fmoc-His(Boc)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Tyr(tBu)-OH. They are

25 dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in

30 *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). At the end of the

synthesis. The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of $\text{Pd(PPh}_3)_4$ dissolved in 5 mL of CHCl_3 :NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl_3 (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL),
5 DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et_2O (Step
10 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H_2O (A) and 0.045% TFA in CH_3CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired
15 modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-48-

DP-178 C

Fmoc-Rink Amide MBHA Resin

Step 1 ↓ SPPS

Boc-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Lys(Aloc)-PSStep 2 ↓ Pd(PPh₃)₄/NMM/HOAc/CHCl₃**Boc-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Lys-PS**

Step 3 ↓ 3-maleimidopropionic acid

Boc-IYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH

Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol

NH₂-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH

TFA

TFA

Example 2

5 Preparation of a Modified DP107--Synthesis of

NNLLRAIEAQQHLLQLTVWQIKQLQARILAVEYLKDQK(MPA)NH₂

In this example, DP107 (SEQ ID NO:2) is synthesized and modified to

include a linker and maleimide group according to the following synthesis scheme. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, DP107 exhibits potent antiviral activity against HIV.

5 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Leu-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Val-OH, Fmoc-Ala-OH, Fmoc-Leu-OH, Fmoc-Ile-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ala-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Gln(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Val-OH, Fmoc-Thr(tBu)-OH, Fmoc-Leu-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-His(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Ala-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Asn(Trt)-OH, Fmoc-Asn(Trt)-OH, They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N'*, *N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and

10 Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). At the end of the synthesis. The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using

20 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by

25

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dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ₂₁₄ and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

DP-107 C

Fmoc-Rink Amide MBHA Resin

Step 1 SPPS

Boc-NNLLRAIEAQQHLLQLTWQIKQLQARILAVERYLKDQ-Lys(Alloc)-PS

Step 2 $\text{Pd}(\text{PPh}_3)_4/\text{NMM}/\text{HOAc}/\text{CHCl}_3$

Boc-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVEERYLKDQ -Lys-PS

Step 3 **3-maleimidopropionic acid**

C(C(=O)Nc1ccc(C(F)(F)F)cc1)C(=O)N[C@@H](Cc2c[nH]cn2)C(=O)N[C@@H](Cc3c[nH]cn3)C(=O)N[C@@H](Cc4c[nH]cn4)C(=O)N[C@@H](Cc5c[nH]cn5)C(=O)N[C@@H](Cc6c[nH]cn6)C(=O)N[C@@H](Cc7c[nH]cn7)C(=O)N[C@@H](Cc8c[nH]cn8)C(=O)N[C@@H](Cc9c[nH]cn9)C(=O)N[C@@H](Cc10c[nH]cn10)C(=O)N[C@@H](Cc11c[nH]cn11)C(=O)N[C@@H](Cc12c[nH]cn12)C(=O)N[C@@H](Cc13c[nH]cn13)C(=O)N[C@@H](Cc14c[nH]cn14)C(=O)N[C@@H](Cc15c[nH]cn15)C(=O)N[C@@H](Cc16c[nH]cn16)C(=O)N[C@@H](Cc17c[nH]cn17)C(=O)N[C@@H](Cc18c[nH]cn18)C(=O)N[C@@H](Cc19c[nH]cn19)C(=O)N[C@@H](Cc20c[nH]cn20)C(=O)N[C@@H](Cc21c[nH]cn21)C(=O)N[C@@H](Cc22c[nH]cn22)C(=O)N[C@@H](Cc23c[nH]cn23)C(=O)N[C@@H](Cc24c[nH]cn24)C(=O)N[C@@H](Cc25c[nH]cn25)C(=O)N[C@@H](Cc26c[nH]cn26)C(=O)N[C@@H](Cc27c[nH]cn27)C(=O)N[C@@H](Cc28c[nH]cn28)C(=O)N[C@@H](Cc29c[nH]cn29)C(=O)N[C@@H](Cc30c[nH]cn30)C(=O)N[C@@H](Cc31c[nH]cn31)C(=O)N[C@@H](Cc32c[nH]cn32)C(=O)N[C@@H](Cc33c[nH]cn33)C(=O)N[C@@H](Cc34c[nH]cn34)C(=O)N[C@@H](Cc35c[nH]cn35)C(=O)N[C@@H](Cc36c[nH]cn36)C(=O)N[C@@H](Cc37c[nH]cn37)C(=O)N[C@@H](Cc38c[nH]cn38)C(=O)N[C@@H](Cc39c[nH]cn39)C(=O)N[C@@H](Cc40c[nH]cn40)C(=O)N[C@@H](Cc41c[nH]cn41)C(=O)N[C@@H](Cc42c[nH]cn42)C(=O)N[C@@H](Cc43c[nH]cn43)C(=O)N[C@@H](Cc44c[nH]cn44)C(=O)N[C@@H](Cc45c[nH]cn45)C(=O)N[C@@H](Cc46c[nH]cn46)C(=O)N[C@@H](Cc47c[nH]cn47)C(=O)N[C@@H](Cc48c[nH]cn48)C(=O)N[C@@H](Cc49c[nH]cn49)C(=O)N[C@@H](Cc50c[nH]cn50)C(=O)N[C@@H](Cc51c[nH]cn51)C(=O)N[C@@H](Cc52c[nH]cn52)C(=O)N[C@@H](Cc53c[nH]cn53)C(=O)N[C@@H](Cc54c[nH]cn54)C(=O)N[C@@H](Cc55c[nH]cn55)C(=O)N[C@@H](Cc56c[nH]cn56)C(=O)N[C@@H](Cc57c[nH]cn57)C(=O)N[C@@H](Cc58c[nH]cn58)C(=O)N[C@@H](Cc59c[nH]cn59)C(=O)N[C@@H](Cc60c[nH]cn60)C(=O)N[C@@H](Cc61c[nH]cn61)C(=O)N[C@@H](Cc62c[nH]cn62)C(=O)N[C@@H](Cc63c[nH]cn63)C(=O)N[C@@H](Cc64c[nH]cn64)C(=O)N[C@@H](Cc65c[nH]cn65)C(=O)N[C@@H](Cc66c[nH]cn66)C(=O)N[C@@H](Cc67c[nH]cn67)C(=O)N[C@@H](Cc68c[nH]cn68)C(=O)N[C@@H](Cc69c[nH]cn69)C(=O)N[C@@H](Cc70c[nH]cn70)C(=O)N[C@@H](Cc71c[nH]cn71)C(=O)N[C@@H](Cc72c[nH]cn72)C(=O)N[C@@H](Cc73c[nH]cn73)C(=O)N[C@@H](Cc74c[nH]cn74)C(=O)N[C@@H](Cc75c[nH]cn75)C(=O)N[C@@H](Cc76c[nH]cn76)C(=O)N[C@@H](Cc77c[nH]cn77)C(=O)N[C@@H](Cc78c[nH]cn78)C(=O)N[C@@H](Cc79c[nH]cn79)C(=O)N[C@@H](Cc80c[nH]cn80)C(=O)N[C@@H](Cc81c[nH]cn81)C(=O)N[C@@H](Cc82c[nH]cn82)C(=O)N[C@@H](Cc83c[nH]cn83)C(=O)N[C@@H](Cc84c[nH]cn84)C(=O)N[C@@H](Cc85c[nH]cn85)C(=O)N[C@@H](Cc86c[nH]cn86)C(=O)N[C@@H](Cc87c[nH]cn87)C(=O)N[C@@H](Cc88c[nH]cn88)C(=O)N[C@@H](Cc89c[nH]cn89)C(=O)N[C@@H](Cc90c[nH]cn90)C(=O)N[C@@H](Cc91c[nH]cn91)C(=O)N[C@@H](Cc92c[nH]cn92)C(=O)N[C@@H](Cc93c[nH]cn93)C(=O)N[C@@H](Cc94c[nH]cn94)C(=O)N[C@@H](Cc95c[nH]cn95)C(=O)N[C@@H](Cc96c[nH]cn96)C(=O)N[C@@H](Cc97c[nH]cn97)C(=O)N[C@@H](Cc98c[nH]cn98)C(=O)N[C@@H](Cc99c[nH]cn99)C(=O)N[C@@H](Cc100c[nH]cn100)C(=O)N[C@@H](Cc101c[nH]cn101)C(=O)N[C@@H](Cc102c[nH]cn102)C(=O)N[C@@H](Cc103c[nH]cn103)C(=O)N[C@@H](Cc104c[nH]cn104)C(=O)N[C@@H](Cc105c[nH]cn105)C(=O)N[C@@H](Cc106c[nH]cn106)C(=O)N[C@@H](Cc107c[nH]cn107)C(=O)N[C@@H](Cc108c[nH]cn108)C(=O)N[C@@H](Cc109c[nH]cn109)C(=O)N[C@@H](Cc110c[nH]cn110)C(=O)N[C@@H](Cc111c[nH]cn111)C(=O)N[C@@H](Cc112c[nH]cn112)C(=O)N[C@@H](Cc113c[nH]cn113)C(=O)N[C@@H](Cc114c[nH]cn114)C(=O)N[C@@H](Cc115c[nH]cn115)C(=O)N[C@@H](Cc116c[nH]cn116)C(=O)N[C@@H](Cc117c[nH]cn117)C(=O)N[C@@H](Cc118c[nH]cn118)C(=O)N[C@@H](Cc119c[nH]cn119)C(=O)N[C@@H](Cc120c[nH]cn120)C(=O)N[C@@H](Cc121c[nH]cn121)C(=O)N[C@@H](Cc122c[nH]cn122)C(=O)N[C@@H](Cc123c[nH]cn123)C(=O)N[C@@H](Cc124c[nH]cn124)C(=O)N[C@@H](Cc125c[nH]cn125)C(=O)N[C@@H](Cc126c[nH]cn126)C(=O)N[C@@H](Cc127c[nH]cn127)C(=O)N[C@@H](Cc128c[nH]cn128)C(=O)N[C@@H](Cc129c[nH]cn129)C(=O)N[C@@H](Cc130c[nH]cn130)C(=O)N[C@@H](Cc131c[nH]cn131)C(=O)N[C@@H](Cc132c[nH]cn132)C(=O)N[C@@H](Cc133c[nH]cn133)C(=O)N[C@@H](Cc134c[nH]cn134)C(=O)N[C@@H](Cc135c[nH]cn135)C(=O)N[C@@H](Cc136c[nH]cn136)C(=O)N[C@@H](Cc137c[nH]cn137)C(=O)N[C@@H](Cc138c[nH]cn138)C(=O)N[C@@H](Cc139c[nH]cn139)C(=O)N[C@@H](Cc140c[nH]cn140)C(=O)N[C@@H](Cc141c[nH]cn141)C(=O)N[C@@H](Cc142c[nH]cn142)C(=O)N[C@@H](Cc143c[nH]cn143)C(=O)N[C@@H](Cc144c[nH]cn144)C(=O)N[C@@H](Cc145c[nH]cn145)C(=O)N[C@@H](Cc146c[nH]cn146)C(=O)N[C@@H](Cc147c[nH]cn147)C(=O)N[C@@H](Cc148c[nH]cn148)C(=O)N[C@@H](Cc149c[nH]cn149)C(=O)N[C@@H](Cc150c[nH]cn150)C(=O)N[C@@H](Cc151c[nH]cn151)C(=O)N[C@@H](Cc152c[nH]cn152)C(=O)N[C@@H](Cc153c[nH]cn153)C(=O)N[C@@H](Cc154c[nH]cn154)C(=O)N[C@@H](Cc155c[nH]cn155)C(=O)N[C@@H](Cc156c[nH]cn156)C(=O)N[C@@H](Cc157c[nH]cn157)C(=O)N[C@@H](Cc158c[nH]cn158)C(=O)N[C@@H](Cc159c[nH]cn159)C(=O)N[C@@H](Cc160c[nH]cn160)C(=O)N[C@@H](Cc161c[nH]cn161)C(=O)N[C@@H](Cc162c[nH]cn162)C(=O)N[C@@H](Cc163c[nH]cn163)C(=O)N[C@@H](Cc164c[nH]cn164)C(=O)N[C@@H](Cc165c[nH]cn165)C(=O)N[C@@H](Cc166c[nH]cn166)C(=O)N[C@@H](Cc167c[nH]cn167)C(=O)N[C@@H](Cc168c[nH]cn168)C(=O)N[C@@H](Cc169c[nH]cn169)C(=O)N[C@@H](Cc170c[nH]cn170)C(=O)N[C@@H](Cc171c[nH]cn171)C(=O)N[C@@H](Cc172c[nH]cn172)C(=O)N[C@@H](Cc173c[nH]cn173)C(=O)N[C@@H](Cc174c[nH]cn174)C(=O)N[C@@H](Cc175c[nH]cn175)C(=O)N[C@@H](Cc176c[nH]cn176)C(=O)N[C@@H](Cc177c[nH]cn177)C(=O)N[C@@H](Cc178c[nH]cn178)C(=O)N[C@@H](Cc179c[nH]cn179)C(=O)N[C@@H](Cc180c[nH]cn180)C(=O)N[C@@H](Cc181c[nH]cn181)C(=O)N[C@@H](Cc182c[nH]cn182)C(=O)N[C@@H](Cc183c[nH]cn183)C(=O)N[C@@H](Cc184c[nH]cn184)C(=O)N[C@@H](Cc185c[nH]cn185)C(=O)N[C@@H](Cc186c[nH]cn186)C(=O)N[C@@H](Cc187c[nH]cn187)C(=O)N[C@@

Step 4 | 85% TFA/5% TIS/5% thioanisole/5% phenol

NCC(N)C(=O)N[C@@H](CCCCNC(C)(C)S(=O)(=O)CCC(C)[NH2])C([NH2+])=O

Example 3**Preparation of a Modified anti-RSV peptide (C terminal)**

In this example, the peptide

5 VITIELSNIKENKCNCAKVKLIKQELDKYKNAV (SEQ ID NO:16) is modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, the native sequence (SEQ ID NO.) inhibits viral infection of respiratory syncytial virus (RSV), including inhibiting fusion and syncytia formation between RSV-infected

10 and uninfected Hep-2 cells.

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are

15 sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Val-OH, Fmoc-Ala-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Gly-OH, Fmoc-

20 Asn(Trt)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Val-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU)

25 and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3

30 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step

2). The resin is then washed with CHCl_3 (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3
5 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et_2O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H_2O (A) and 0.045% TFA in CH_3CN (B)) over 180 min at 9.5
10 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ_{214} and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

Fmoc-Rink Amide MBHA Resin

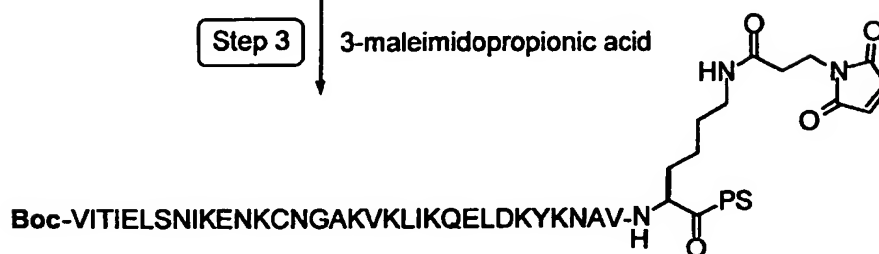
Step 1 ↓ **SPPS**

Boc-VITIELSNIKENKCNGAKVKLIKQELDKYKNAV-Lys(Alloc)-PS

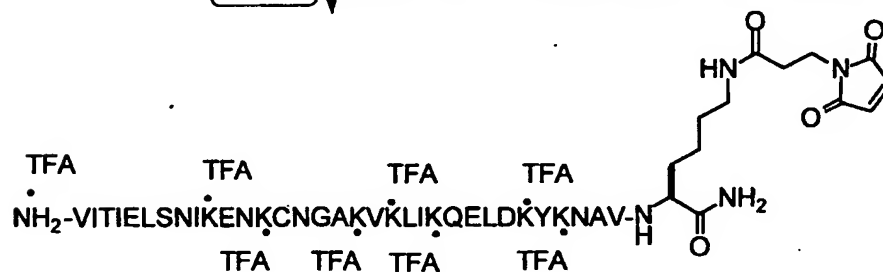
Step 2 ↓ $\text{Pd(PPh}_3)_4/\text{NMM/HOAc/CHCl}_3$

Boc-VITIELSNIKENKCNGAKVKLIKQELDKYKNAV-Lys -PS

Step 3 **3-maleimidopropionic acid**



Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol



TFA

TEA

TEA

TEA

TFA

TFA

TFA

TFA

Example 4**Preparation of a Modified anti-RSV peptide (T-N terminal)**

In this example, the peptide

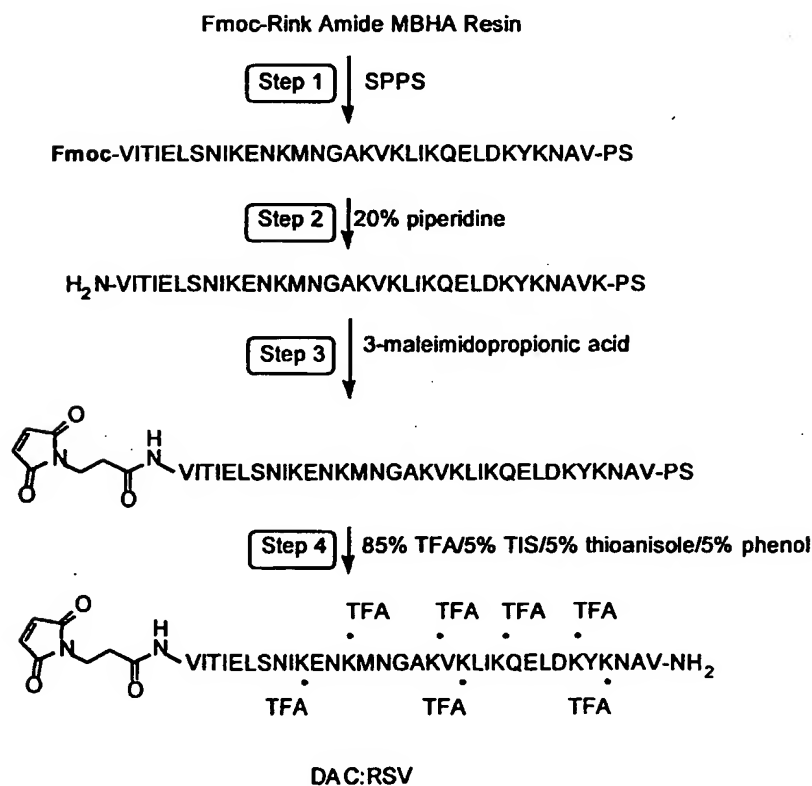
5 VITIELSNIKENKCNGAKVKLIKQELDKYKNAV (SEQ ID NO:17), which corresponds to the peptide of SEQ ID NO:16 but where a Cysteine (C) has been substituted for the Methionine (M), residue is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, the native sequence
10 (SEQ ID NO:16) inhibits viral infection of respiratory syncytial virus (RSV), including inhibiting fusion and syncytia formation between RSV-infected and uninfected Hep-2 cells.

15 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Val-OH, Fmoc-Ala-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asp(tBu)-
20 OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Gly-OH, Fmoc-Asn(Trt)-OH, **Fmoc-Met-OH**, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Leu-
25 OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Val-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N,N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of
30 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The synthesis is then re-automated for the addition of the 3-maleimidopropionic

acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by

5 preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95%

10 purity, as determined by RP-HPLC.



Example 5**Preparation of a Modified anti-RSV peptide**

5 In this example, the peptide SEQ ID NO:14 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:14 inhibits viral infection of respiratory syncytial virus (RSV), including inhibiting fusion and syncytia formation between RSV-infected and uninfected Hep-2 cells.

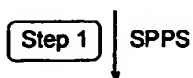
10

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Gly-OH, Fmoc-Asn(Trt)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Val-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Tyr(tBu)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N,N*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated

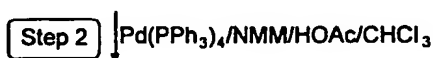
30

for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

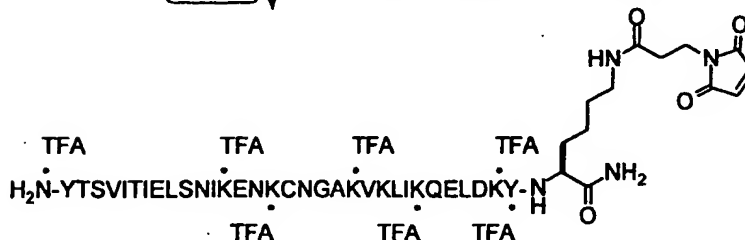
Fmoc-Rink Amide MBHA Resin



Boc-YTSVITIELSNIKENKCNGAKVKLIKQELDKY-Lys(Alloc)-PS



Boc-YTSVITIELSNIKENKCNGAKVKLIKQELDKY-Lys-PS



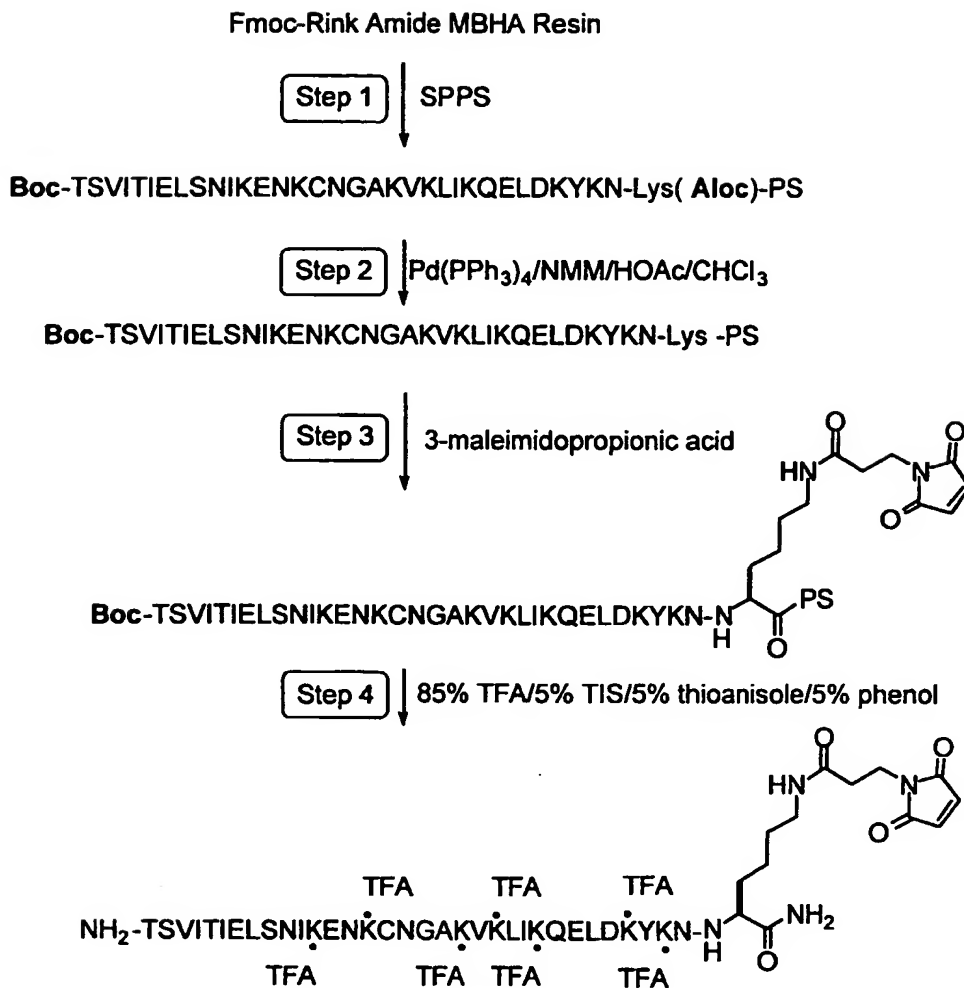
Example 6 (T-143)**Preparation of a Modified anti-RSV peptide**

5 In this example, the peptide SEQ ID NO:15 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:15 inhibits viral infection of respiratory syncytial virus (RSV), including inhibiting fusion and syncytia formation between RSV-infected and uninfected Hep-2 cells.

10 Solid phase peptide synthesis of the modified peptide analog on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Gly-OH, Fmoc-Asn(Trt)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Val-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃, (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6

x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-60-

**Example 7****5 Preparation of a Modified anti-RSV peptide (C Terminal)**

In this example, the peptide SEQ ID NO:17), which corresponds to SEQ ID NO:16 with a cysteine (C) substituted for the Methionine (M), is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, the native sequence SEQ ID NO:16. inhibits viral infection of respiratory syncytial

10

virus (RSV), including inhibiting fusion and syncytia formation between RSV-infected and uninfected Hep-2 cells.

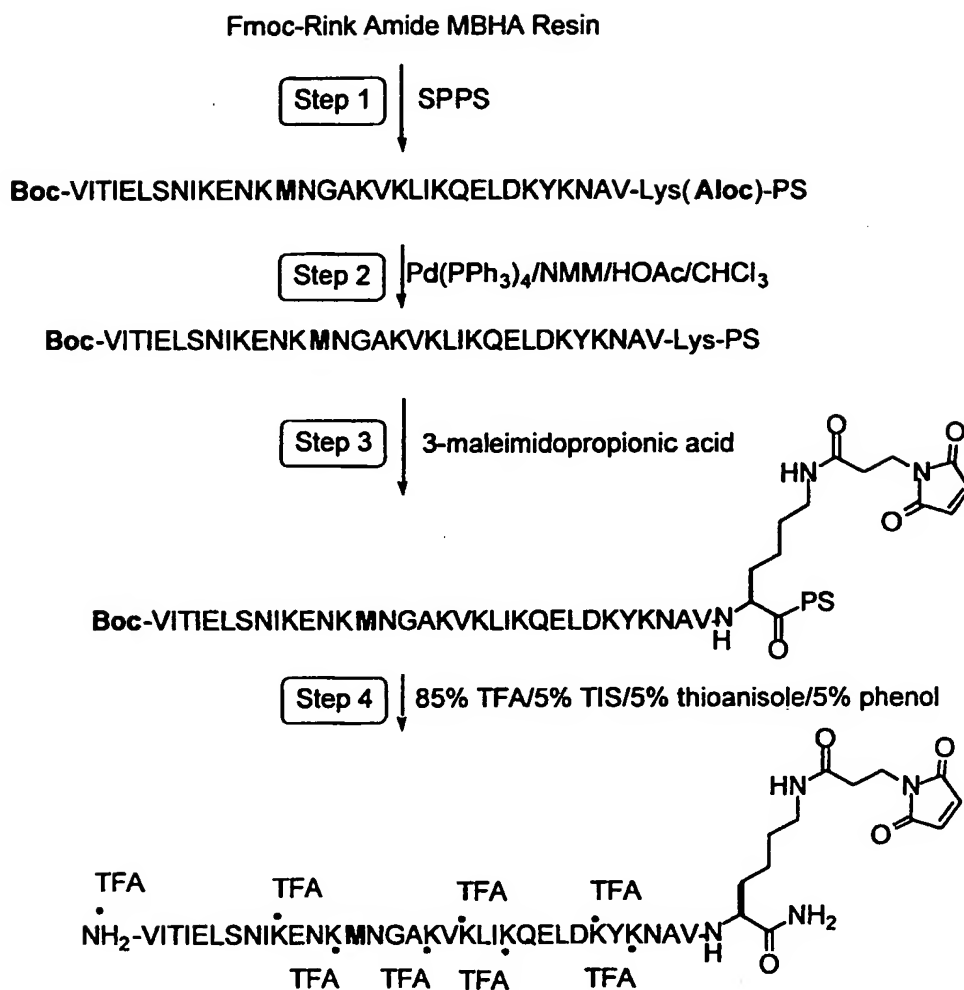
Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Val-OH, Fmoc-Ala-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Gly-OH, Fmoc-Asn(Trt)-OH, **Fmoc-Met-OH**, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Val-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N'*,*N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of $\text{Pd(PPh}_3)_4$ dissolved in 5 mL of CHCl_3 :NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl_3 (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et_2O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045%

TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

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-63-



Example 8
Preparation of a Modified anti-RSV peptide

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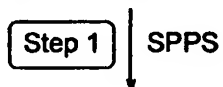
In this example, the peptide SEQ ID NO:29. is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:29 inhibits viral infection of respiratory syncytial virus (RSV), including inhibiting fusion and syncytia formation between RSV-infected and uninfected Hep-2 cells.

10

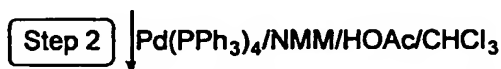
Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Leu-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Leu-OH, Fmoc-Val-OH, Fmoc-Ser(tBu)-OH, Fmoc-Val-OH, Fmoc-Gly-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Leu-OH, Fmoc-Ser(tBu)-OH, Fmoc-Val-OH, Fmoc-Val-OH, Fmoc-Ala-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Ile-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide

(i.e., DAC) in >95% purity, as determined by RP-HPLC.

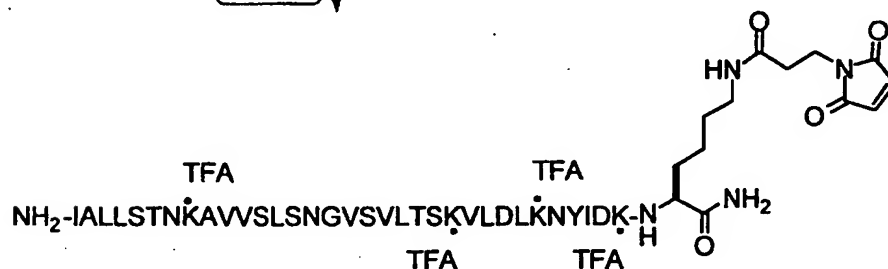
Fmoc-Rink Amide MBHA Resin



Boc-IALLSTNKAVVSLNNGVSVLT SKVLDLKNYIDK-Lys(Alloc)-PS



Boc-IALLSTNKAVVSLNNGVSVLT SKVLDLKNYIDK-Lys -PS



Example 9 (T-173)

5 Preparation of a Modified anti-HPIV peptide

In this example, the peptide SEQ ID NO:52. is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:52 inhibits viral infection of human parainfluenza virus 3 (HPIV3), including

10 inhibiting fusion and syncytia formation between HPIV3-infected Hep2 cells and

uninfected CV-1W cells.

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Val-OH, Fmoc-Ser(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Val-OH, Fmoc-Ala-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ile-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ala-OH, Fmoc-Gln(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Val-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N,N*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex

Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

Fmoc-Rink Amide MBHA Resin

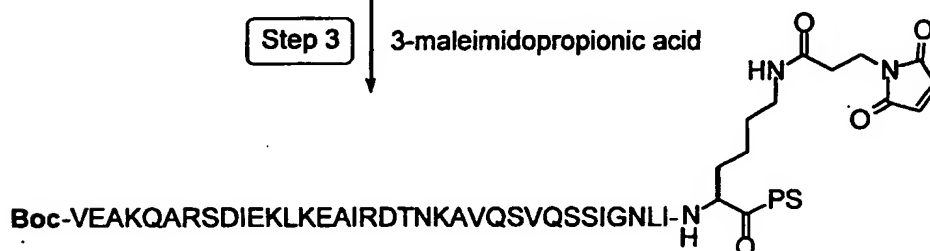
Step 1 **SPPS**

Boc-VEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI-Lys(Alloc)-PS

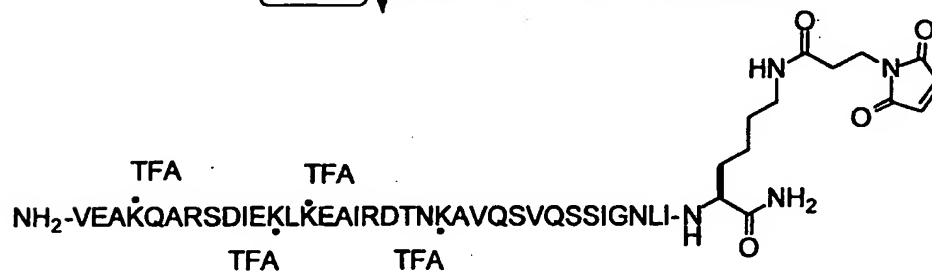
Step 2 | $\text{Pd}(\text{PPh}_3)_4/\text{NMM}/\text{HOAc}/\text{CHCl}_3$

Boc-VEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI-Lys -PS

Step 3 3-maleimidopropionic acid



Step 4 | 85% TFA/5% TIS/5% thioanisole/5% phenol



Example 10**Preparation of a Modified anti-HPIV peptide**

In this example, the peptide SEQ ID NO:58 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:58 inhibits viral infection of human parainfluenza virus 3 (HPIV3), including inhibiting fusion and syncytia formation between HPIV3-infected Hep2 cells and uninfected CV-1W cells.

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Val-OH, Fmoc-Ser(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Ala-OH, Fmoc-Val-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Val-OH, Fmoc-Ser(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Val-OH, Fmoc-Ala-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ile-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Arg(Pbf)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of $\text{Pd(PPh}_3)_4$ dissolved in 5 mL of CHCl_3 :NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with

CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

Fmoc-Rink Amide MBHA Resin

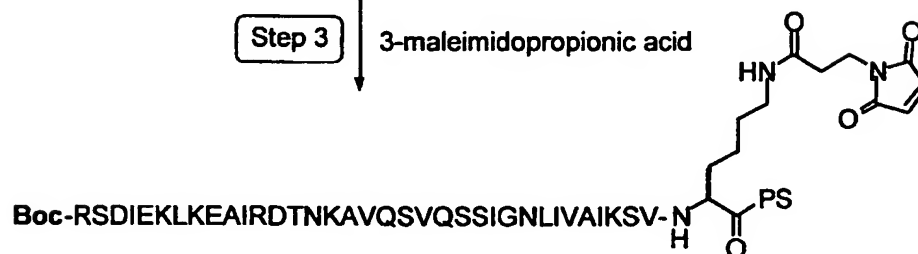
Step 1 SPPS

Boc-RSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAISKV-Lys(Alloc)-PS

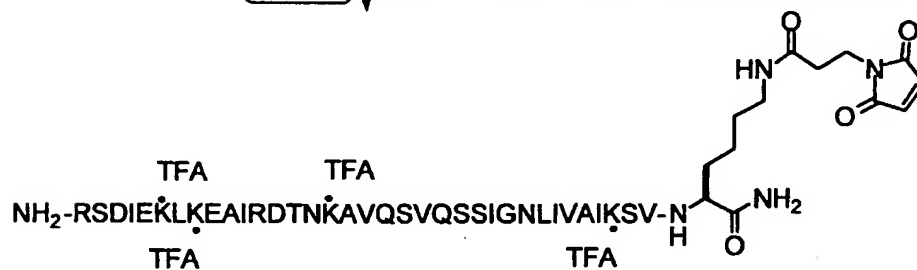
Step 2 | $\text{Pd}(\text{PPh}_3)_4/\text{NMM}/\text{HOAc}/\text{CHCl}_3$

Boc-RSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSV-Lys -PS

Step 3 **3-maleimidopropionic acid**



Step 4 | 85% TFA/5% TIS/5% thioanisole/5% phenol



TFA

TFA

TFA

TFA

Example 11**Preparation of a Modified anti-HPIV peptide**

5 In this example, the peptide SEQ ID NO:35 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:35 inhibits viral infection of human parainfluenza virus 3 (HPIV3), including inhibiting fusion and syncytia formation between HPIV3-infected Hep2 cells and uninfected CV-1W cells.

10

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Leu-OH, Fmoc-
15 Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ile-OH, Fmoc-Trp(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Ile-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ser(tBu)-OH,
20 Fmoc-Ile-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ile-OH, Fmoc-Pro-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Val-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asn(Trt)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3
30 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step

2). The resin is then washed with CHCl_3 (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3
5 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et_2O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H_2O (A) and 0.045% TFA in CH_3CN (B)) over 180 min at 9.5
10 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-73-

Fmoc-Rink Amide MBHA Resin

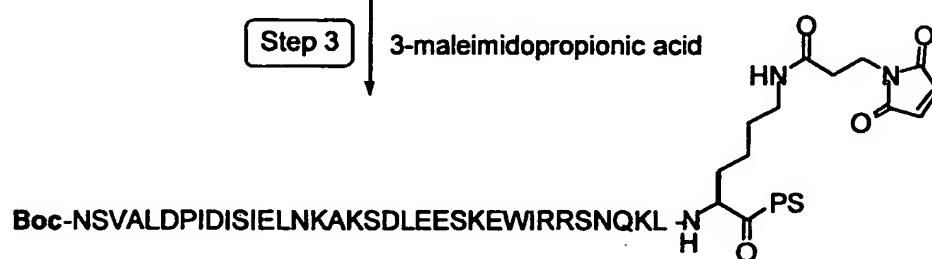
Step 1 ↓ SPPS

Boc-NSVALDPIDISIELNKAQSDLEESKEWIRRSNQKL -Lys(Aloc)-PS

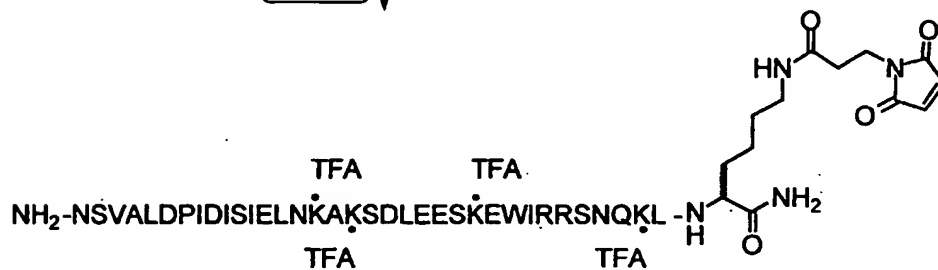
Step 2 ↓ Pd(PPh₃)₄/NMM/HOAc/CHCl₃

Boc-NSVALDPIDISIELNKAQSDLEESKEWIRRSNQKL -Lys-PS

Step 3 ↓ 3-maleimidopropionic acid



Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol



Example 12**Preparation of a Modified anti-HPIV peptide**

5 In this example, the peptide SEQ ID NO:38 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO: 38 inhibits viral infection of human parainfluenza virus 3 (HPIV3), including inhibiting fusion and syncytia formation between HPIV3-infected Hep2 cells and uninfected CV-1W cells.

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Solid phase peptide synthesis of the modified peptide analog on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ile-OH, Fmoc-Trp(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ile-OH, Fmoc-Pro-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, BOC-Lys(Aloc)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N,N*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed

15

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25

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with CHCl_3 (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et_2O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H_2O (A) and 0.045% TFA in CH_3CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-76-

Fmoc-Rink Amide MBHA Resin

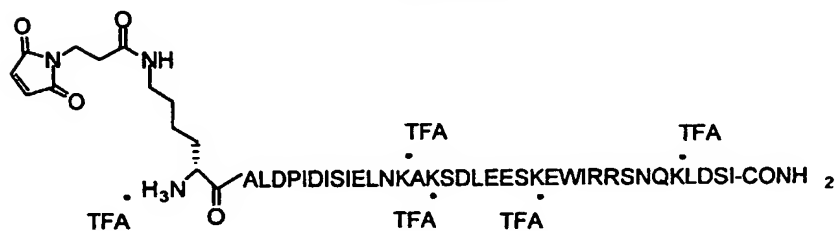
Step 1 | SPPS

Boc-Lys(Aloc)-ALDPIDISIELNKA⁺SDLEESKEWIRRSNQKLD⁺SI-PSStep 2 | Pd(PPh₃)₄/NMM/HOAc/CHCl₃Boc-Lys-ALDPIDISIELNKA⁺SDLEESKEWIRRSNQKLD⁺SI-PS

Step 3 | 3-maleimidopropionic acid



Step 4 | 85% TFA/5% TIS/5% thioanisole/5% phenol



Example 13**Preparation of a Modified anti-HPIV peptide**

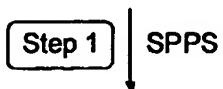
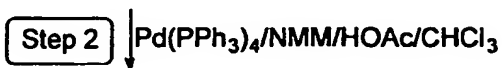
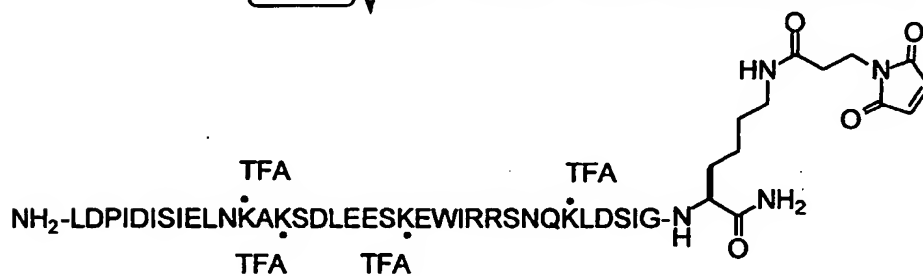
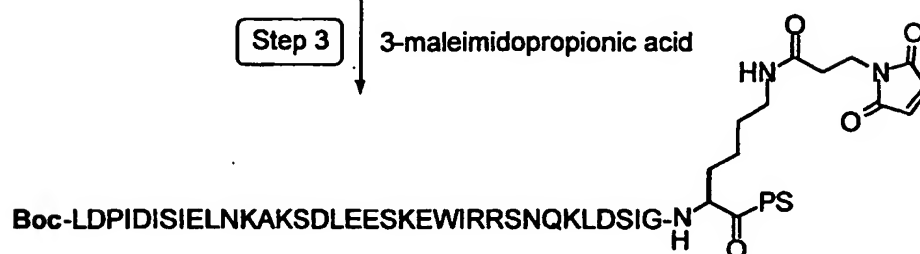
5 In this example, the peptide SEQ ID NO:39 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:39 inhibits viral infection of human parainfluenza virus 3 (HPIV3), including inhibiting fusion and syncytia formation between HPIV3-infected Hep2 cells and
10 uninfected CV-1W cells.

 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are
15 sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gly-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ile-OH, Fmoc-Trp(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-
20 OH, Fmoc-Leu-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ile-OH, Fmoc-Pro-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the
25 sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the
30 resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of

CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3
5 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and
10 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-79-

Fmoc-Rink Amide MBHA Resin

**Boc-LDPIDISIELNKAQSDLEESKEWIRRSNQKLD SIG-Lys(Alloc)-PS****Boc-LDPIDISIELNKAQSDLEESKEWIRRSNQKLD SIG-Lys-PS**

Example 14**Preparation of a Modified anti-HPIV peptide**

5 In this example, the peptide SEQ ID NO:40 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO. inhibits viral infection of human parainfluenza virus 3 (HPIV3), including inhibiting fusion and syncytia formation between HPIV3-infected Hep2 cells and
10 uninfected CV-1W cells.

 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected
15 amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gly-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ile-OH, Fmoc-Trp(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ser(tBu)-OH,
20 Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ile-OH, Fmoc-Pro-OH, Fmoc-Asp(tBu)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and,
25 according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and
30 accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed

with CHCl_3 (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et_2O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H_2O (A) and 0.045% TFA in CH_3CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

Example 15**Preparation of a Modified anti-HPIV peptide**

5 In this example, the peptide SEQ ID NO:41 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:41 inhibits viral infection of human parainfluenza virus 3 (HPIV3), including inhibiting fusion and syncytia formation between HPIV3-infected Hep2 cells and
10 uninfected CV-1W cells.

 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected
15 amino acids are sequentially added to resin: Fmoc-Trp(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gly-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ile-OH, Fmoc-Trp(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ser(tBu)-OH,
20 Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ile-OH, Fmoc-Pro-OH, Boc-Lys(Aloc)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and,
25 according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and
30 accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed

with CHCl_3 (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The

5 peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et_2O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H_2O (A) and 0.045% TFA in CH_3CN (B)) over 180 min at 9.5 mL/min using a Phenomenex

10 Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

Fmoc-Rink Amide MBHA Resin

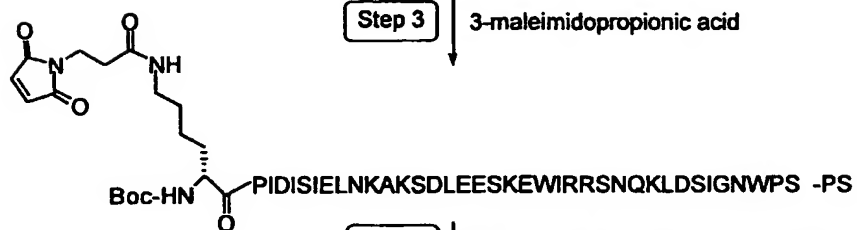
Step 1 SPPS

Boc-Lys(Aloc)-PIDISIELNKA₂SDLEESKEWIRRSNQKLDSIGNW-PS

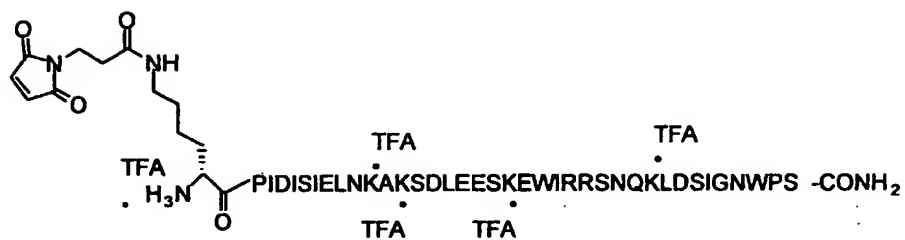
Step 2 $\text{Pd}(\text{PPh}_3)_4/\text{NMM}/\text{HOAc}/\text{CHCl}_3$

Boc-Lys-PIDISIELNKA KSDLEESKEWIRRSNQKLDSIGNWPS

Step 3 **3-maleimidopropionic acid**



Step 4 | 85% TFA/5% TIS/5% thioanisole/5% phenol



Example 16**Preparation of a Modified anti-HPIV peptide**

5 In this example, the peptide SEQ ID NO:42 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:42 inhibits viral infection of human parainfluenza virus 3 (HPIV3), including inhibiting fusion and syncytia formation between HPIV3-infected Hep2 cells and
10 uninfected CV-1W cells.

 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are
15 sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-His(Boc)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gly-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ile-OH, Fmoc-Trp(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-
20 OH, Fmoc-Ser(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Lys(Boc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Ile-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ile-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and,
25 according to the sequence, activated using O-benzotriazol-1-yl-*N,N,N,N*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and
30 accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in

5 mL of CHCl_3 :NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl_3 (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3
5 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et_2O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H_2O (A) and
10 0.045% TFA in CH_3CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC

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Fmoc-Rink Amide MBHA Resin

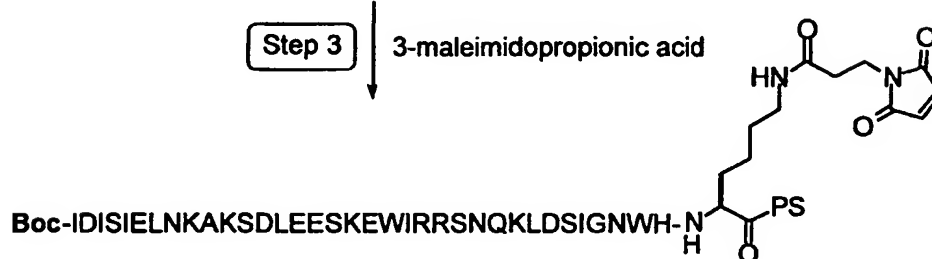
Step 1 | **SPPS**

Boc-IDISIELNKAKSDLEESKEWIRRSNQKLDSIGNWH-Lys(Alloc)-PS

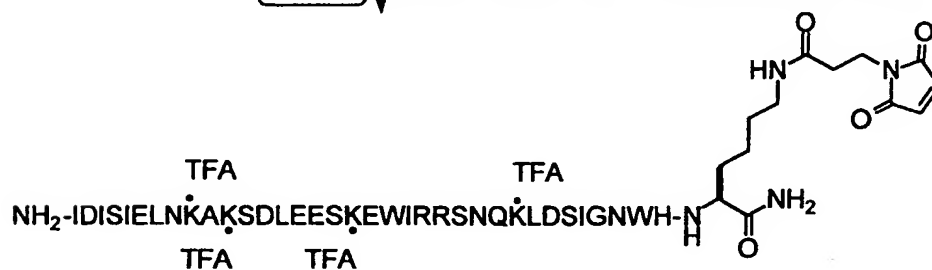
Step 2 ↓ $\text{Pd(PPh}_3)_4/\text{NMM/HOAc/CHCl}_3$

Boc-IDISIELNKA KSDLEESKEWIRRSNQKLDSIGNWH-Lys-PS

Step 3 3-maleimidopropionic acid



Step 4 | 85% TFA/5% TIS/5% thioanisole/5% phenol



TFA

TFA

TFA

TFA

Example 17**Preparation of a Modified anti-MeV peptide**

5 In this example, the peptide SEQ ID NO:77. is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:77 inhibits viral infection of measles virus (MeV), including inhibiting fusion and syncytia formation between MeV-infected and uninfected Vero cells.

10

 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Ile-OH, Fmoc-Ala-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Asn(Trt)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Gly-OH, Fmoc-Val-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ile-OH, Fmoc-Pro-OH, Fmoc-Pro-OH, Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ile-OH, Fmoc-Arg(Pbf)-OH, Fmoc-His(Boc)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N,N*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and

30

DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

Fmoc-Rink Amide MBHA Resin

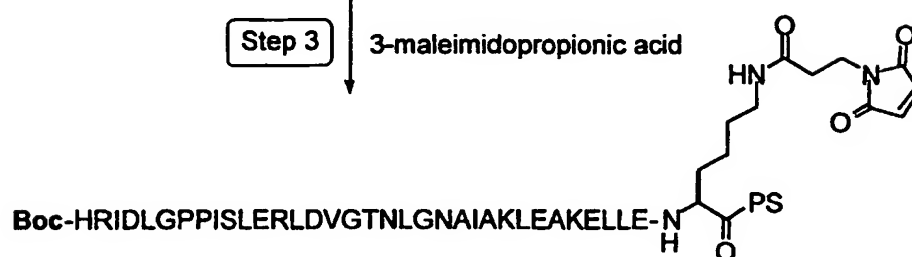
Step 1 SPPS

Boc-HRIDLGPPISLERLDVGTNLGNIAKLEAKELLE-Lys(Alloc)-PS

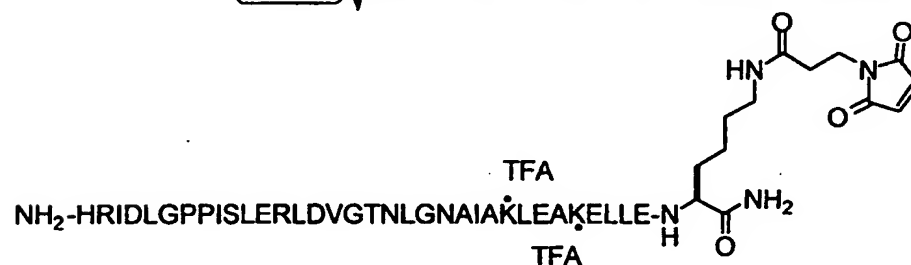
Step 2 | $\text{Pd}(\text{PPh}_3)_4/\text{NMM}/\text{HOAc}/\text{CHCl}_3$

Boc-HRIDLGPPISLERLDVGTNLGNIAKLEAKELLE-Lys-PS

Step 3 **3-maleimidopropionic acid**



Step 4 | 85% TFA/5% TIS/5% thioanisole/5% phenol



Example 18**Preparation of a Modified anti-MeV peptide**

5 In this example, the peptide SEQ ID NO:79 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:79 inhibits viral infection of measles virus (MeV), including inhibiting fusion and syncytia formation between MeV-infected and uninfected Vero cells.

10 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-
15 Ser(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Ile-OH, Fmoc-Ala-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Asn(Trt)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Gly-OH, Fmoc-Val-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-
20 OH, Fmoc-Arg(Pbf)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ile-OH, Fmoc-Pro-OH, Fmoc-Pro-OH, Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ile-OH, They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and
25 Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2).
30 The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL),

DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC

-94-

Fmoc-Rink Amide MBHA Resin

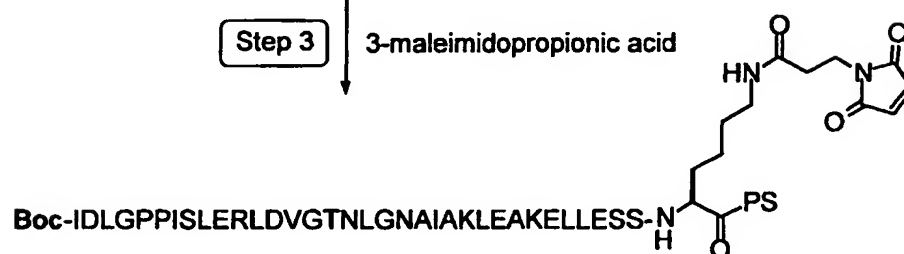
Step 1 ↓ SPPS

Boc-IDLGPPISLERLDVGTNLGNAIAKLEAKELLESS-Lys(Alloc)-PS

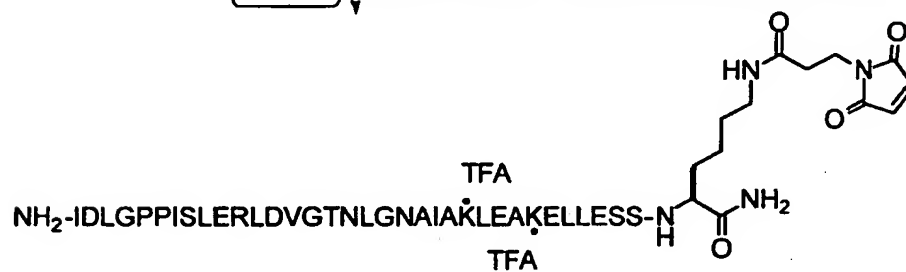
Step 2 ↓ Pd(PPh₃)₄/NMM/HOAc/CHCl₃

Boc-IDLGPPISLERLDVGTNLGNAIAKLEAKELLESS-Lys-PS

Step 3 ↓ 3-maleimidopropionic acid



Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol



Example 19**Preparation of a Modified anti-MeV peptide**

5 In this example, the peptide SEQ ID NO:81 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO: 79 inhibits viral infection of measles virus (MeV), including inhibiting fusion and syncytia formation between MeV-infected and uninfected Vero cells.

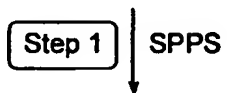
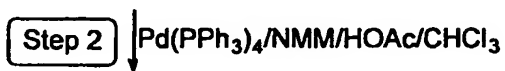
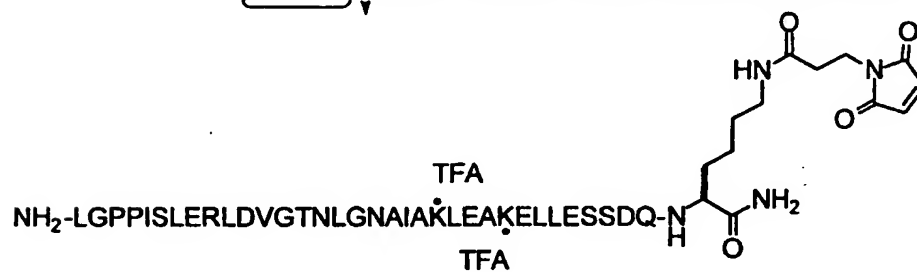
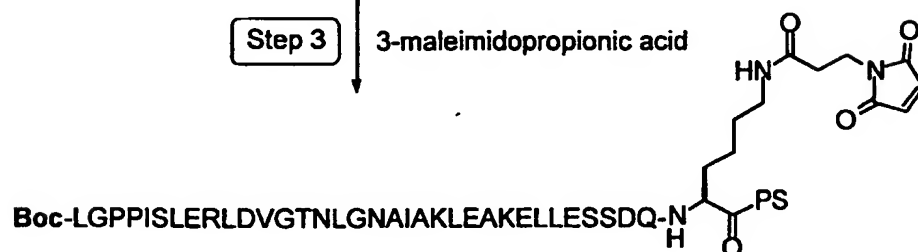
10

 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Ile-OH, Fmoc-Ala-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Asn(Trt)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Gly-OH, Fmoc-Val-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ile-OH, Fmoc-Pro-OH, Fmoc-Pro-OH, Fmoc-Gly-OH, Fmoc-Leu-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N'*, *N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the

addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-97-

Fmoc-Rink Amide MBHA Resin

**Boc-LGPPISLERLDVGTNLGNAIAKLEAKELLESSDQ-Lys(Alloc)-PS****Boc-LGPPISLERLDVGTNLGNAIAKLEAKELLESSDQ-Lys-PS**

Example 20**Preparation of a Modified anti-MeV peptide**

5 In this example, the peptide SEQ ID NO:84 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:84 inhibits viral infection of measles virus (MeV), including inhibiting fusion and syncytia formation between MeV-infected and uninfected Vero cells.

10

 Solid phase peptide synthesis of the modified peptide on a 100 µmole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Leu-
15 OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ala-OH, Fmoc-Ile-OH, Fmoc-Ala-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Asn(Trt)-OH, Fmoc-
20 Thr(tBu)-OH, Fmoc-Gly-OH, Fmoc-Val-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Ser(tBu)-OH, Fmoc-Ile-OH, Fmoc-Pro-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N'*, *N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and
25 Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2).
30 The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the

addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

Fmoc-Rink Amide MBHA Resin

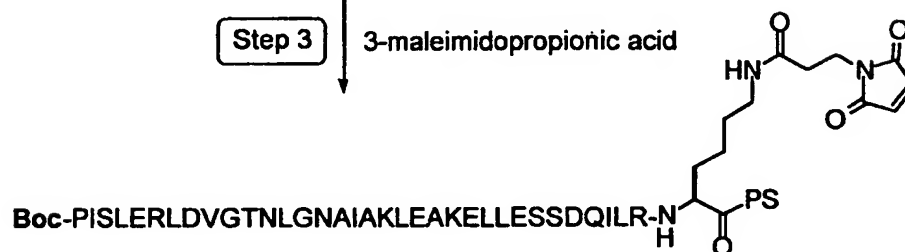
Step 1 ↓ **SPPS**

Boc-PISLERLDVGTNLGNIAKLEAKELLESSDQILR-Lys(Alloc)-PS

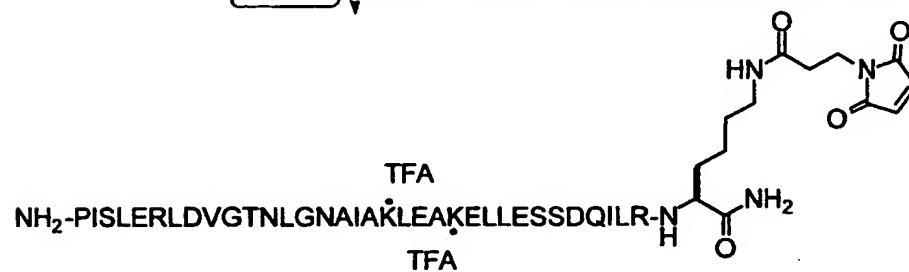
Step 2 ↓ Pd(PPh₃)₄/NMM/HOAc/CHCl₃

Boc-PISLERLDVGTNLGNAIAKLEAKELLESSDQILR-Lys -PS

Step 3 ↓ **3-maleimidopropionic acid**



Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol



TFA

TFA

Example 21**Preparation of a Modified anti-SIV peptide**

5 In this example, the peptide SEQ ID NO:64 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:64 exhibits potent antiviral activity as a crude peptide against simian immunodeficiency virus (SIV).

10 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Phe-OH, Fmoc-Asp(tBu)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Trp(Boc)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed

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25

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with CHCl_3 (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The

5 peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et_2O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H_2O (A) and 0.045% TFA in CH_3CN (B)) over 180 min at 9.5 mL/min using a Phenomenex

10 Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

Fmoc-Rink Amide MBHA Resin

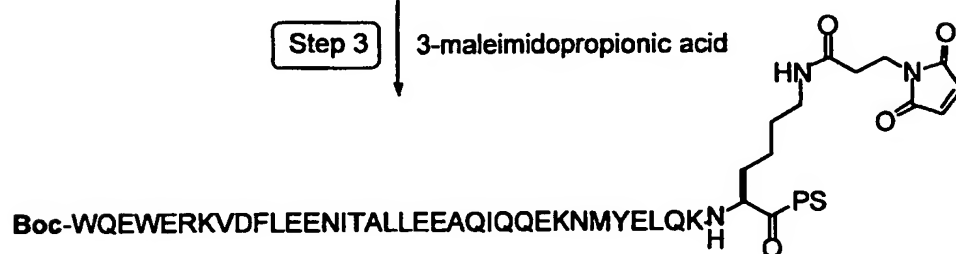
Step 1 **SPPS**

Boc-WQEWKVDLFLEENITALLEEAQIQQEKNMYELQK-Lys(Alloc)-PS

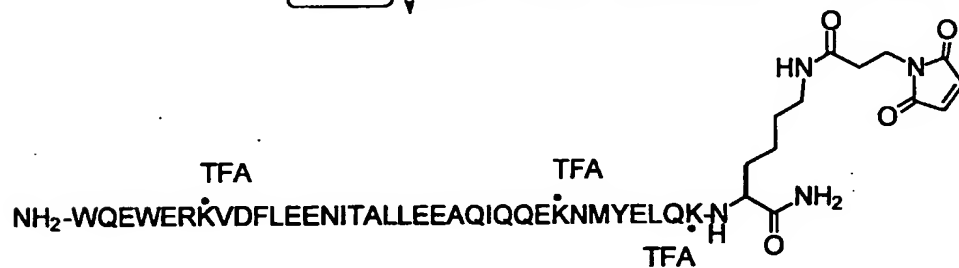
Step 2 ↓ Pd(PPh₃)₄/NMM/HOAc/CHCl₃

Boc-WQEWERKVDFLEENITALLEEAQIQQEKNMYELQK-Lys-PS

Step 3 ↓ 3-maleimidopropionic acid



Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol



TFA

TFA

TFA

Example 22**Preparation of a Modified anti-SIV peptide**

5 In this example, the peptide SEQ ID NO:65 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:65 exhibits potent antiviral activity as a crude peptide against simian immunodeficiency virus (SIV).

10 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Leu-OH, Fmoc-

15 Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH,

20 Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Phe-OH, Fmoc-Asp(tBu)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N,N*-

25 tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in

30 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and

DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-106-

Fmoc-Rink Amide MBHA Resin

Step 1

SPPS

Boc-QEWERKVDLFLEENITALLEEAIQQEKNMYELQKL-Lys(Alloc)-PS

Step 2

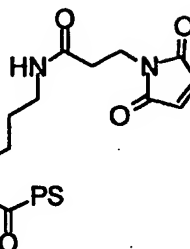
 $\text{Pd(PPh}_3)_4/\text{NMM/HOAc/CHCl}_3$

Boc-QEWERKVDLFLEENITALLEEAIQQEKNMYELQKL-Lys-PS

Step 3

3-maleimidopropionic acid

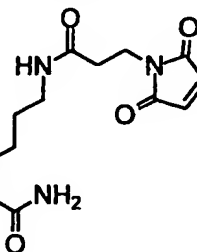
Boc-QEWERKVDLFLEENITALLEEAIQQEKNMYELQKL-NH



Step 4

85% TFA/5% TIS/5% thioanisole/5% phenol

TFA
 NH₂-QEWERKVDLFLEENITALLEEAIQQEKNMYELQKL-NH
 TFA
 TFA



Example 23**Preparation of a Modified anti-SIV peptide**

5 In this example, the peptide SEQ ID NO:66 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:66 exhibits potent antiviral activity as a crude peptide against simian immunodeficiency virus (SIV).

10 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Phe-OH, Fmoc-Asp(tBu)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Glu(tBu)-OH Boc-Lys(Aloc)-OH,. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using O-benzotriazol-1-yl-*N, N, N', N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of

20 CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with

25 CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6

30

x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-109-

Fmoc-Rink Amide MBHA Resin

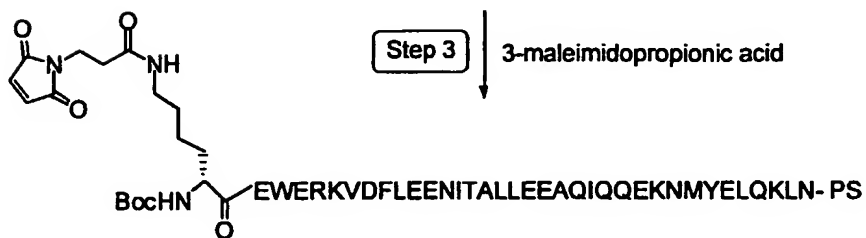
Step 1 ↓ SPPS

Boc-Lys(Aloc)-EWEKVFLEENITALLEEAIQQEKNMYELQKLN-PS

Step 2 ↓ Pd(PPh₃)₄/NMM/HOAc/CHCl₃

Boc-Lys-EWEKVFLEENITALLEEAIQQEKNMYELQKLN-PS

Step 3 ↓ 3-maleimidopropionic acid



Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol



Example 24**Preparation of a Modified anti-SIV peptide**

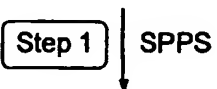
In this example, the peptide SEQ ID NO:67 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:67 exhibits potent antiviral activity as a crude peptide against simian immunodeficiency virus (SIV).

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Phe-OH, Fmoc-Asp(tBu)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Trp(Boc)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and

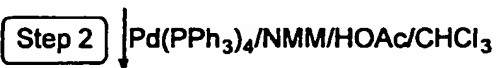
DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-112-

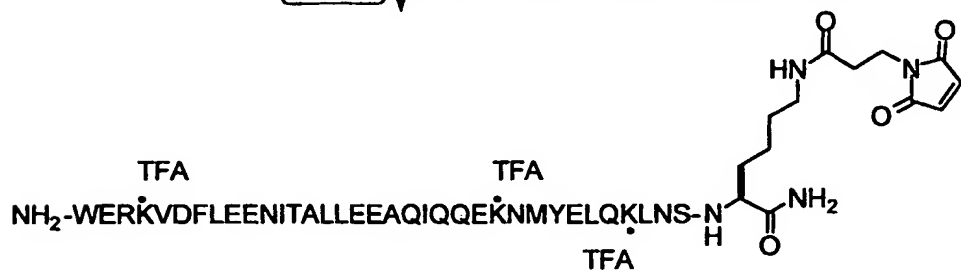
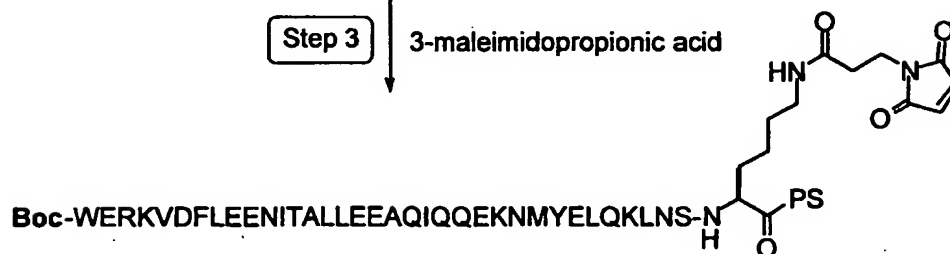
Fmoc-Rink Amide MBHA Resin



Boc-WERKVDLFLEENITALLEEAIQQEKNMYELQKLNS-Lys(Alloc)-PS



Boc-WERKVDLFLEENITALLEEAIQQEKNMYELQKLNS-Lys-PS



Example 25**Preparation of a Modified anti-SIV peptide**

In this example, the peptide SEQ ID NO:68 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:68 exhibits potent antiviral activity as a crude peptide against simian immunodeficiency virus (SIV).

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Trp(Boc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Phe-OH, Fmoc-Asp(tBu)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Glu(tBu)-OH, Boc-Lys(Aloc)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and

DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-115-

Fmoc-Rink Amide MBHA Resin

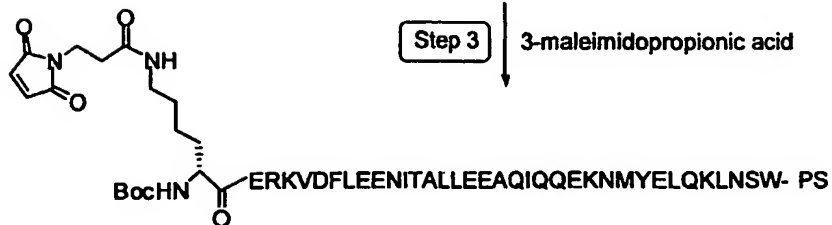
Step 1 ↓ SPPS

Boc-Lys(Aloc)-ERKVDFLEENITALLEEAIQQEKNMYELQKLNSW -PS

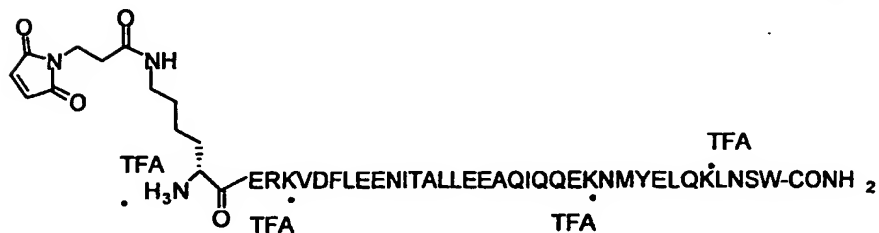
Step 2 ↓ Pd(PPh₃)₄/NMM/HOAc/CHCl₃

Boc-Lys-ERKVDFLEENITALLEEAIQQEKNMYELQKLNSW- PS

Step 3 ↓ 3-maleimidopropionic acid



Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol



Example 26**Preparation of a Modified anti-SIV peptide**

In this example, the peptide SEQ ID NO:69 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:69 exhibits potent antiviral activity as a crude peptide against simian immunodeficiency virus (SIV).

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Phe-OH, Fmoc-Asp(tBu)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Fmoc-Arg(Pbf)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N,N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and

DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-118-

Fmoc-Rink Amide MBHA Resin

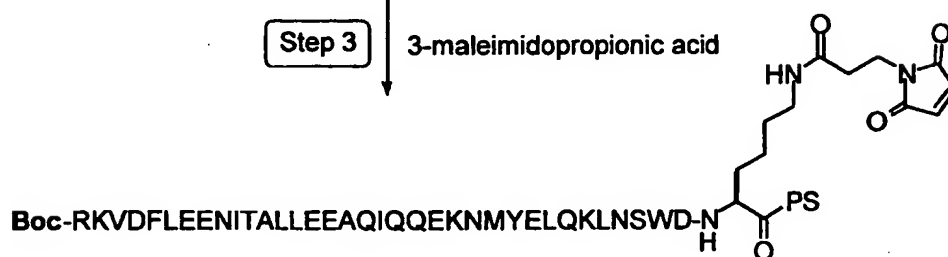
Step 1 ↓ SPPS

Boc-RKVDFLEENITALLEEAIQQEKNMYELQKLNSWD-Lys(Alloc)-PS

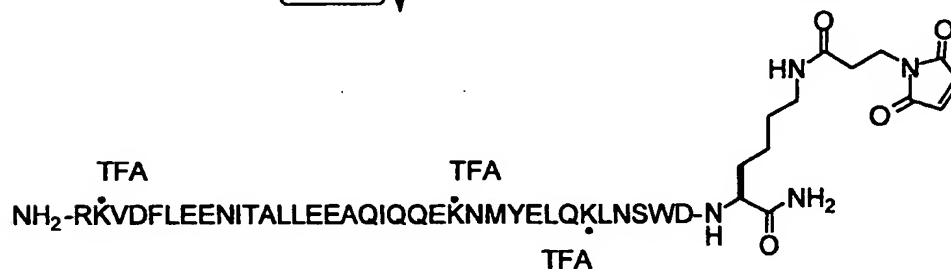
Step 2 ↓ Pd(PPh₃)₄/NMM/HOAc/CHCl₃

Boc-RKVDFLEENITALLEEAIQQEKNMYELQKLNSWD-Lys-PS

Step 3 ↓ 3-maleimidopropionic acid



Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol



Example 27**Preparation of a Modified anti-SIV peptide**

5 In this example, the peptide SEQ ID NO:70. is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:70 exhibits potent antiviral activity as a crude peptide against simian immunodeficiency virus (SIV).

10

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Val-OH, Fmoc-Asp(tBu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Phe-OH, Fmoc-Asp(tBu)-OH, Fmoc-Val-OH, Fmoc-Lys(Boc)-OH, Boc-Lys(Aloc)-OH,. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of

30

CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3
5 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and
10 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-121-

Fmoc-Rink Amide MBHA Resin

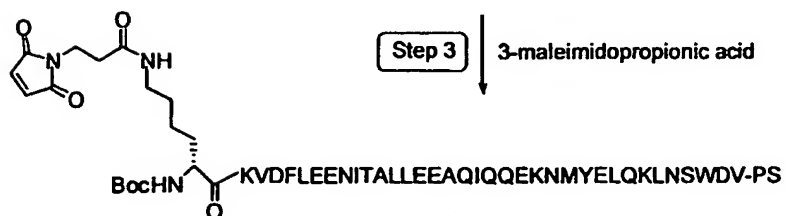
Step 1 ↓ SPPS

Boc-Lys(Aloc)-KVDLFLEENITALLEEAIQQEKNMYELQKLNSWDV-Lys(Aloc)-PS

Step 2 ↓ Pd(PPh₃)₄/NMM/HOAc/CHCl₃

Boc-Lys-KVDLFLEENITALLEEAIQQEKNMYELQKLNSWDV-PS

Step 3 ↓ 3-maleimidopropionic acid



Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol



Example 28**Preparation of a Modified anti-SIV peptide**

5 In this example, the peptide SEQ ID NO:71 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:71 exhibits potent antiviral activity as a crude peptide against simian immunodeficiency virus (SIV).

10

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Phe-OH, Fmoc-Val-OH, 15 Fmoc-Asp(tBu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, 20 Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Phe-OH, Fmoc-Asp(tBu)-OH, Fmoc-Val-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the 25 Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of 30 CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with

CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The

5 peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex

10 Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

Fmoc-Rink Amide MBHA Resin

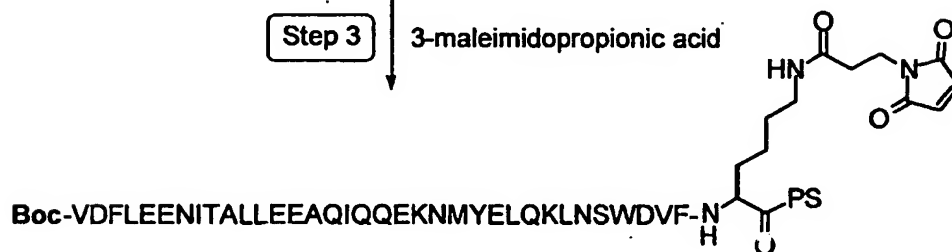
Step 1 ↓ SPSS

Boc-VDFLEENITALLLEAAQIQQEKNMYELQKLNSWDVF-Lys(Alloc)-PS

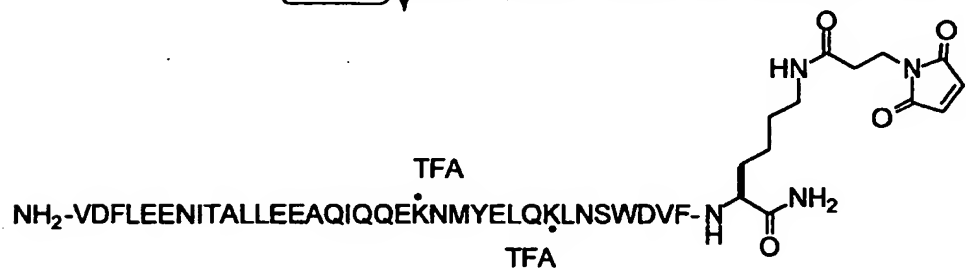
Step 2 ↓ $\text{Pd(PPh}_3)_4/\text{NMM/HOAc/CHCl}_3$

Boc-VDFLEENITALLEEAQIQQEKNMYELQKLNSWDVF-Lys -PS

Step 3 ↓ **3-maleimidopropionic acid**



Step 4 ↓ 85% TFA/5% TIS/5% thioanisole/5% phenol



TFA

TFA

Example 29**Preparation of a Modified anti-SIV peptide**

5 In this example, the peptide SEQ ID NO:72 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:72 exhibits potent antiviral activity as a crude peptide against simian immunodeficiency virus (SIV).

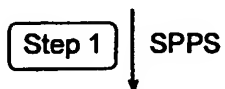
10

Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Gly-OH, Fmoc-Phe-OH, 15 Fmoc-Val-OH, Fmoc-Asp(tBu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, 20 Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Phe-OH, Fmoc-Asp(tBu)-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium 25 hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of Pd(PPh₃)₄ dissolved in 5 mL of 30 CHCl₃:NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with

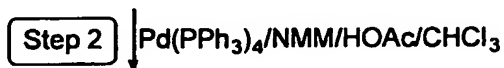
CHCl₃ (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6 x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

-127-

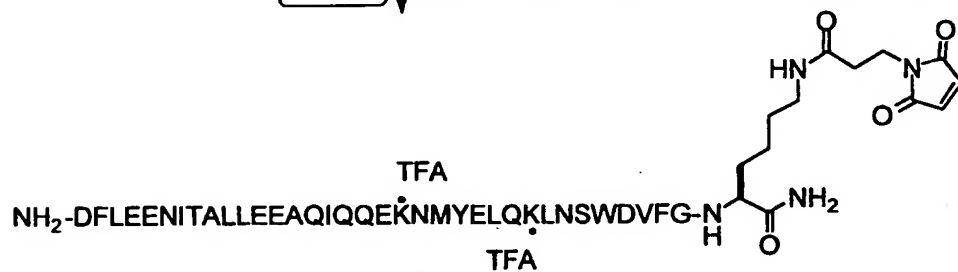
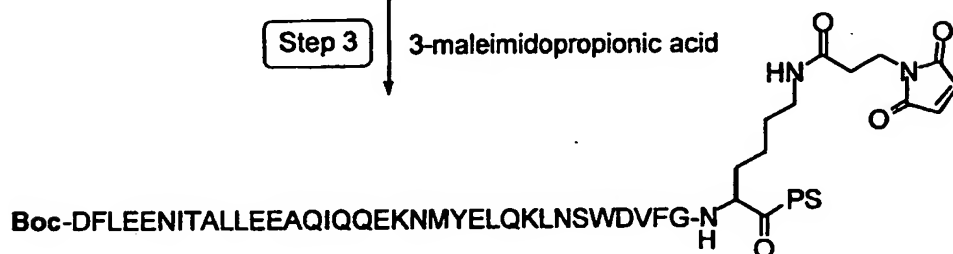
Fmoc-Rink Amide MBHA Resin



Boc-DFLEENITALLEEAQIQQEKNMYELQKLNSWDVFG-Lys(Alloc)-PS



Boc-DFLEENITALLEEAQIQQEKNMYELQKLNSWDVFG-Lys-PS



Example 30**Preparation of a Modified anti-SIV peptide**

5 In this example, the peptide SEQ ID NO:73 is synthesized and modified to include a linker and maleimide group according to the synthesis scheme set forth below. As reported in U.S. Pat. Nos. 6,013,236 and 6,020,459, SEQ ID NO:73 exhibits potent antiviral activity as a crude peptide against simian immunodeficiency virus (SIV).

10 Solid phase peptide synthesis of the modified peptide on a 100 μ mole scale is performed using manual solid-phase synthesis, a Symphony Peptide Synthesizer and Fmoc protected Rink Amide MBHA. The following protected amino acids are sequentially added to resin: Fmoc-Lys(Aloc)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gly-OH, Fmoc-Phe-OH, Fmoc-Val-OH, Fmoc-Asp(tBu)-OH, Fmoc-Trp(Boc)-OH, 15 Fmoc-Ser(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Glu(tBu)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ala-OH, Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Thr(tBu)-OH, Fmoc-Ile-OH, Fmoc-Asn(Trt)-OH, 20 Fmoc-Glu(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Leu-OH, Fmoc-Phe-OH. They are dissolved in *N,N*-dimethylformamide (DMF) and, according to the sequence, activated using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and Diisopropylethylamine (DIEA). Removal of the 25 Fmoc protecting group is achieved using a solution of 20% (V/V) piperidine in *N,N*-dimethylformamide (DMF) for 20 minutes (step 1). The selective deprotection of the Lys (Aloc) group is performed manually and accomplished by treating the resin with a solution of 3 eq of $\text{Pd}(\text{PPh}_3)_4$ dissolved in 5 mL of CHCl_3 :NMM:HOAc (18:1:0.5) for 2 h (Step 2). The resin is then washed with 30 CHCl_3 (6 x 5 mL), 20% HOAc in DCM (6 x 5 mL), DCM (6 x 5 mL), and DMF (6

x 5 mL). The synthesis is then re-automated for the addition of the 3-maleimidopropionic acid (Step 3). Between every coupling, the resin is washed 3 times with *N,N*-dimethylformamide (DMF) and 3 times with isopropanol. The peptide is cleaved from the resin using 85% TFA/5% TIS/5% thioanisole and 5% phenol, followed by precipitation by dry-ice cold Et₂O (Step 4). The product is purified by preparative reversed phased HPLC using a Varian (Rainin) preparative binary HPLC system: gradient elution of 30-55% B (0.045% TFA in H₂O (A) and 0.045% TFA in CH₃CN (B)) over 180 min at 9.5 mL/min using a Phenomenex Luna 10 μ phenyl-hexyl, 21 mm x 25 cm column and UV detector (Varian Dynamax UVD II) at λ 214 and 254 nm to afford the desired modified peptide (i.e., DAC) in >95% purity, as determined by RP-HPLC.

Fmoc-Rink Amide MBHA Resin

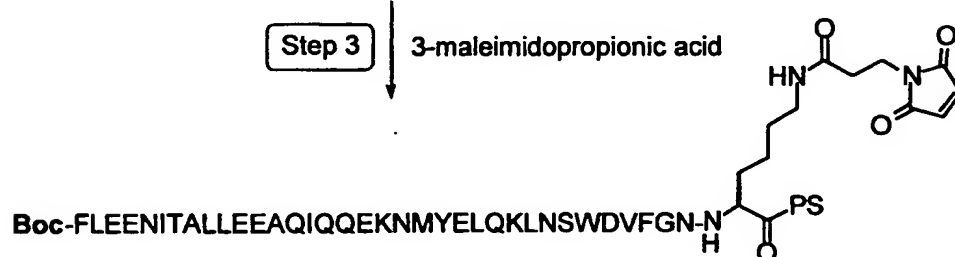
Step 1 SPPS

Boc-FLEENITALLEEAQIQQEKNMYELQKLNSWDVFGN-Lys(Alloc)-PS

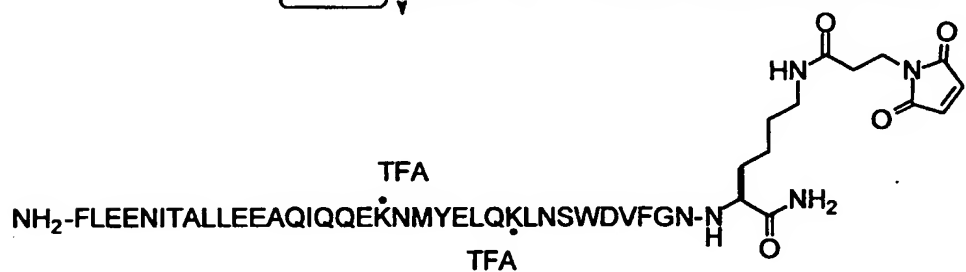
Step 2 $\text{Pd(PPh}_3)_4/\text{NMM/HOAc/CHCl}_3$

Boc-FLEENITALLEEAQIQQEKNMYELQKLNSWDVFGN-Lys-PS

Step 3 **3-maleimidopropionic acid**



Step 4 | 85% TFA/5% TIS/5% thioanisole/5% phenol



TFA

TFA

While certain embodiments of the invention have been described and exemplified, those having ordinary skill in the art will understand that the invention is not intended to be limited to the specifics of any of these embodiments, but is rather defined by the accompanying claims.

TABLE 2

DP178 CARBOXY TRUNCATIONS	
5	YTS YTSL YTSLI YTSLIH YTSLIHS
10	YTSLIHSL YTSLIHSLI YTSLIHSLIE YTSLIHSLIFE YTSLIHSLIEES
15	YTSLIHSLIEESQ YTSLIHSLIEESQN YTSLIHSLIEESQNNQ YTSLJHSLJEEESQNNQ YTSLIHSLIEESQNNQEQ
20	YTSLIHSLIEESQNNQEQEK YTSLIHSLIEESQNNQEQKN YTSLIHSLIEESQNNQEQKNE YTSLIHSLIEESQNNQEQKNEQ YTSLIHSLIEESQNNQEQKNEQE
25	YTSLIHSLIEESQNNQEQKNEQEL YTSLIHSLIEESQNNQEQKNEQELL YTSLIHSLIEESQNNQEQKNEQELLE YTSLIHSLIEESQNNQEQKNEQELLEL YTSLIHSLIEESQNNQEQKNEQELLELD
30	YTSLIHSLIEESQNNQEQKNEQELLELDK

YTSLIHSLIEESQNQQEKNEQELLELDKW
YTSLIHSLIEESQNQQEKNEQELLELDKWA
YTSLIHSLIEESQNQQEKNEQELLELDKWAS
YTSLIHSLIEESQNQQEKNEQELLELDKWASL
5 YTSLIHSLIEESQNQQEKNEQELLELDKWASLW
YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN
YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW
YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF

10 The one letter amino acid code of Table 1 is used.

TABLE 3

DP178 AMINO TRUNCATIONS	
5	NWF
	WNWF
	LWNWF
	SLWNWF
10	ASLWNWF
	WASLWNWF
	KWASLWNWF
	DKWASLWNWF
	LDKWASLWNWF
15	ELDKWASLWNWF
	LELDKWASLWNWF
	LLELDKWASLWNWF
	ELLELDKWASLWNWF
	QELLELDKWASLWNWF
20	EQELLELDKWASLWNWF
	NEQELLELDKWASLWNWF
	KNEQELLELDKWASLWNWF
	EKNEQELLELDKWASLWNWF
	QEKNEQELLELDKWASLWNWF
25	QQEKNEQELLELDKWASLWNWF
	NQQEKNEQELLELDKWASLWNWF
	QNQQEKNEQELLELDKWASLWNWF
	SQNQQEKNEQELLELDKWASLWNWF
	ESQNQQEKNEQELLELDKWASLWNWF
30	EESQNQQEKNEQELLELDKWASLWNWF

IEESQNQQEKNEQEELLELDKWASLWNWF
LIEESQNQQEKNEQEELLELDKWASLWNWF
SLIEESQNQQEKNEQEELLELDKWASLWNWF
HSLIEESQNQQEKNEQEELLELDKWASLWNWF
5 IHSLIEESQNQQEKNEQEELLELDKWASLWNWF
LIHSLIEESQNQQEKNEQEELLELDKWASLWNWF
SLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF
TSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF
YTSLIHSLIEESQNQQEKNEQEELLELDKWASLWNWF

10

The one letter amino acid code of Table 1 is used.

TABLE 4

DP107 CARBOXY TRUNCATIONS	
<hr/>	
5	NNL
	NNLL
	NNLLR
	NNLLRA
	NNLLRAI
10	NNLLRAIE
	NNLLRAIEA
	NNLLRAIEAQ
	NNLLRAIEAQQ
	NNLLRAIEAQQH
15	NNLLRAIEAQQHL
	NNLLRAIEAQQHLL
	NNLLRAIEAQQHLLQ
	NNLLRAIEAQQHLLQL
	NNLLRAIEAQQHLLQLT
20	NNLLRAIEAQQHLLQLTV
	NNLLRAIEAQQHLLQLTVW
	NNLLRAIEAQQHLLQLTVWQ
	NNLLRAIEAQQHLLQLTVWQI
	NNLLRAIEAQQHLLQLTVWQIK
25	NNLLRAIEAQQHLLQLTVWQIKQ
	NNLLRAIEAQQHLLQLTVWQIKQL
	NNLLRAIEAQQHLLQLTVWQIKQLQ
	NNLLRAIEAQQHLLQLTVWQIKQLQA
	NNLLRAIEAQQHLLQLTVWQIKQLQAR
30	NNLLRAIEAQQHLLQLTVWQIKQLQARI

TABLE 5

DP107 AMINO TRUNCATIONS	
5	KDQ LKDQ YLKDQ RYLKDQ ERYLKDQ
10	VERYLKDQ AVERYLKDQ LAVERYLKDQ ILAVERYLKDQ RILAVERYLKDQ
15	ARILAVERYLKDQ QARILAVERYLKDQ LQARILAVERYLKDQ QLQARILAVERYLKDQ KQLQARILAVERYLKDQ
20	IKQLQARILAVERYLKDQ QIKQLQARILAVERYLKDQ WQIKQLQARILAVERYLKDQ VWQIKQLQARILAVERYLKDQ TVWQIKQLQARILAVERYLKDQ
25	LTVWQIKQLQARILAVERYLKDQ QLTVWQIKQLQARILAVERYLKDQ LQLTVWQIKQLQARILAVERYLKDQ LLQLTVWQIKQLQARILAVERYLKDQ HLLQLTVWQIKQLQARILAVERYLKDQ
30	QHLLQLTVWQIKQLQARILAVERYLKDQ

QQHLLQLTVWQIKQLQARILAVERYLKDQ
AQHLLQLTVWQIKQLQARILAVERYLKDQ
EAQQHLLQLTVWQIKQLQARILAVERYLKDQ
IEAQHLLQLTVWQIKQLQARILAVERYLKDQ
5 AIEAQHLLQLTVWQIKQLQARILAVERYLKDQ
RAIEAQHLLQLTVWQIKQLQARILAVERYLKDQ
LRAIEAQHLLQLTVWQIKQLQARILAVERYLKDQ
LLRAIEAQHLLQLTVWQIKQLQARILAVERYLKDQ
NLLRAIEAQHLLQLTVWQIKQLQARILAVERYLKDQ
10 NNLLRAIEAQHLLQLTVWQIKQLQARILAVERYLKDQ

The one letter amino acid code of Table 1 is used.

TABLE 6

HIV-2 _{NH2} DP178 analog carboxy truncations.	
<hr/>	
5	LEA
	LEAN
	LEANI
	LEANIS
	LEANISQ
10	LEANISQS
	LEANISQSL
	LEANISQSLE
	LEANISQSLEQ
	LEANISQSLEQA
15	LEANISQSLEQAQ
	LEANISQSLEQAQI
	LEANISQSLEQAQIQ
	LEANISQSLEQAQIQQ
	LEANISQSLEQAQIQQE
20	LEANISQSLEQAQIQQEK
	LEANISQSLEQAQIQQEKN
	LEANISQSLEQAQIQQEKNM
	LEANISQSLEQAQIQQEKNMY
	LEANISQSLEQAQIQQEKNMYE
25	LEANISQSLEQAQIQQEKNMYEL
	LEANISQSLEQAQIQQEKNMYELQ
	LEANISQSLEQAQIQQEKNMYELQK
	LEANISQSLEQAQIQQEKNMYELQKL
	LEANISQSLEQAQIQQEKNMYELQKLN
30	LEANISQSLEQAQIQQEKNMYELQKLNS

LEANISQSLEQAQIQQEKNMYELQKLNSW
LEANISQSLEQAQIQQEKNMYELQKLNSWD
LEANISQSLEQAQIQQEKNMYELQKLNSWDV
LEANISQSLEQAQIQQEKNMYELQKLNSWDVF
5 LEANISQSLEQAQIQQEKNMYELQKLNSWDVFT
LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTN
LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNW
LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL

10 The one letter amino acid code of Table 1 is used.

TABLE 7

HIV-2 _{NH2} DP178 analog amino truncations.	
<hr/>	
5	NWL
	TNWL
	FTNWL
	VFTNWL
	DVFTNWL
10	WDVFTNWL
	SWDVFTNWL
	NSWDVFTNWL
	LNSWDVFTNWL
	KLNSWDVFTNWL
15	QKLNSWDVFTNWL
	LQKLNSWDVFTNWL
	ELQKLNSWDVFTNWL
	YELQKLNSWDVFTNWL
	MYELQKLNSWDVFTNWL
20	NMYELQKLNSWDVFTNWL
	KNMYELQKLNSWDVFTNWL
	EKNMYELQKLNSWDVFTNWL
	QEKNMYELQKLNSWDVFTNWL
	QQEKNMYELQKLNSWDVFTNWL
25	IQQEKNMYELQKLNSWDVFTNWL
	QIQQEKNMYELQKLNSWDVFTNWL
	AQIQQEKNMYELQKLNSWDVFTNWL
	QAAIQQEKNMYELQKLNSWDVFTNWL
	EQAAIQQEKNMYELQKLNSWDVFTNWL
30	LEAAIQQEKNMYELQKLNSWDVFTNWL

SLEQAQIQQEKNMYELQKLNSWDVFTNWL
QSLEQAQIQQEKNMYELQKLNSWDVFTNWL
SQSLEQAQIQQEKNMYELQKLNSWDVFTNWL
ISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL
5 NISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL
ANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL
EANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL
LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL

10 The one letter amino acid code of Table 1 is used.

TABLE 8

RESPIRATORY SYNCYTIAL VIRUS (RSV) DP107 F2 REGION ANALOG CARBOXY TRUNCATIONS	
5	YTS
	YTSV
	YTSVI
	YTSVIT
10	YTSVITI
	YTSVITIE
	YTSVITIEL
	YTSVITIELS
	YTSVITIELSN
15	YTSVITIELSNI
	YTSVITIELSNIK
	YTSVITIELSNIKE
	YTSVITIELSNIKEN
	YTSVITIELSNIKENK
20	YTSVITIELSNIKENKC
	YTSVITIELSNIKENKCN
	YTSVITIELSNIKENKCNG
	YTSVITIELSNIKENKCNGT
	YTSVITIELSNIKENKCNGTD
25	YTSVITIELSNIKENKCNGTDA
	YTSVITIELSNIKENKCNGTDAK
	YTSVITIELSNIKENKCNGTDAKV
	YTSVITIELSNIKENKCNGTDAKVK
	YTSVITIELSNIKENKCNGTDAKVKL
30	YTSVITIELSNIKENKCNGTDAKVCLI

YTSVITIELSNIKENKCNGTDAKVKLIK
YTSVITIELSNIKENKCNGTDAKVKLIKQ
YTSVITIELSNIKENKCNGTDAKVKLIKQE
YTSVITIELSNIKENKCNGTDAKVKLIKQEL
5 YTSVITIELSNIKENKCNGTDAKVKLIKQELD
YTSVITIELSNIKENKCNGTDAKVKLIKQELDK
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKY
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYK
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKN
10 YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNA
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAV
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAV
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTE
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTEL
15 YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQ
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQL
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLL
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLM
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQ
20 YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQS
YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST

The one letter amino acid code of Table 1 is used.

TABLE 9

RESPIRATORY SYNCYTIAL VIRUS (RSV) DP107 F2 REGION ANALOG AMINO TRUNCATIONS	
5	QST
	MQST
	LMQST
	LLMQST
10	QLLMQST
	LQLLMQST
	ELQLLMQST
	TELQLLMQST
	VTELQLLMQST
15	AVTELQLLMQST
	NAVTELQLLMQST
	KNAVTELQLLMQST
	YKNAVTELQLLMQST
	KYKNAVTELQLLMQST
20	DKYKNAVTELQLLMQST
	LDKYKNAVTELQLLMQST
	ELDKYKNAVTELQLLMQST
	QELDKYKNAVTELQLLMQST
	KQELDKYKNAVTELQLLMQST
25	IKQELDKYKNAVTELQLLMQST
	LIKQELDKYKNAVTELQLLMQST
	KLIKQELDKYKNAVTELQLLMQST
	VKLIKQELDKYKNAVTELQLLMQST
	KVKLIKQELDKYKNAVTELQLLMQST
30	AKVKLIKQELDKYKNAVTELQLLMQST

DAKVKLIKQELDKYKNAVTELQLLMQST
TDAKVKLIKQELDKYKNAVTELQLLMQST
GTDAKVKLIKQELDKYKNAVTELQLLMQST
NGTDAKVKLIKQELDKYKNAVTELQLLMQST
5 CNGTDAKVKLIKQELDKYKNAVTELQLLMQST
KCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
NKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
KENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
IKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
10 NIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
SNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
LSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
ELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
IELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
15 TIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
ITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
VITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
SVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
TSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST
20

The one letter amino acid code of Table 1 is used.

TABLE 10

RESPIRATORY SYNCYTIAL VIRUS (RSV) F1 DP178 REGION ANALOG CARBOXY TRUNCATIONS	
5	FYD
	FYDP
	FYDPL
	FYDPLV
10	FYDPLVF
	FYDPLVFP
	FYDPLVFPS
	FYDPLVFPSD
	FYDPLVFPSDE
15	FYDPLVFPSDEF
	FYDPLVFPSDEFD
	FYDPLVFPSDEFDA
	FYDPLVFPSDEFDAS
	FYDPLVFPSDEFDASI
20	FYDPLVFPSDEFDASIS
	FYDPLVFPSDEFDASISQ
	FYDPLVFPSDEFDASISQV
	FYDPLVFPSDEFDASISQVN
	FYDPLVFPSDEFDASISQVNE
25	FYDPLVFPSDEFDASISQVNEK
	FYDPLVFPSDEFDASISQVNEKI
	FYDPLVFPSDEFDASISQVNEKIN
	FYDPLVFPSDEFDASISQVNEKINQ
	FYDPLVFPSDEFDASISQVNEKINQS
30	FYDPLVFPSDEFDASISQVNEKINQSL

FYDPLVFPSDEFDASISQVNEKINQSLA
FYDPLVFPSDEFDASISQVNEKINQSLAF
FYDPLVFPSDEFDASISQVNEKINQSLAFI
FYDPLVFPSDEFDASISQVNEKINQSLAFIR
5 FYDPLVFPSDEFDASISQVNEKINQSLAFIRK
FYDPLVFPSDEFDASISQVNEKINQSLAFIRKS
FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSD
FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDE
FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL
10 FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDELL

The one letter amino acid code of Table 1 is used.

TABLE 11

RESPIRATORY SYNCYTIAL VIRUS (RSV) F1 DP178	
REGION ANALOG AMINO TRUNCATIONS	
5	DELL
	SDELL
	KSDELL
	RKSDELL
10	IRKSDELL
	FIRKSDELL
	AFIRKSDELL
	LAFIRKSDELL
	SLAFIRKSDELL
15	QSLAFIRKSDELL
	NQSLAFIRKSDELL
	INQSLAFIRKSDELL
	KINQSLAFIRKSDELL
	EKINQSLAFIRKSDELL
20	NEKINQSLAFIRKSDELL
	VNEKINQSLAFIRKSDELL
	QVNEKINQSLAFIRKSDELL
	SQVNEKINQSLAFIRKSDELL
	ISQVNEKINQSLAFIRKSDELL
25	SISQVNEKINQSLAFIRKSDELL
	ASISQVNEKINQSLAFIRKSDELL
	DASISQVNEKINQSLAFIRKSDELL
	FDASISQVNEKINQSLAFIRKSDELL
	EFDASISQVNEKINQSLAFIRKSDELL
30	DEFDASISQVNEKINQSLAFIRKSDELL

SDEFDASISQVNEKINQSLAFIRKSDELL
PSDEFDASISQVNEKINQSLAFIRKSDELL
FPSDEFDASISQVNEKINQSLAFIRKSDELL
VFPSDEFDASISQVNEKINQSLAFIRKSDELL
5 LVFPSDEFDASISQVNEKINQSLAFIRKSDELL
PLVFPSDEFDASISQVNEKINQSLAFIRKSDELL
DPLVFPSDEFDASISQVNEKINQSLAFIRKSDELL
YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDELL

10 The one letter amino acid code of Table 1 is used.

TABLE 12

HUMAN PARAINFLUENZA VIRUS 3 (HPV3) F1 REGION DP178 ANALOG CARBOXY TRUNCATIONS	
5	ITL
	ITLN
	ITLNN
	ITLNNS
10	ITLNNSV
	ITLNNSVA
	ITLNNSVAL
	ITLNNSVALD
	ITLNNSVALDP
15	ITLNNSVALDPI
	ITLNNSVALDPID
	ITLNNSVALDPIDI
	ITLNNSVALDPIDIS
	ITLNNSVALDPIDISI
20	ITLNNSVALDPIDISIE
	ITLNNSVALDPIDISIEL
	ITLNNSVALDPIDISIELN
	ITLNNSVALDPIDISIELNK
	ITLNNSVALDPIDISIELNKA
25	ITLNNSVALDPIDISIELNKAK
	ITLNNSVALDPIDISIELNKAKS
	ITLNNSVALDPIDISIELNKAKSD
	ITLNNSVALDPIDISIELNKAKSDL
	ITLNNSVALDPIDISIELNKAKSDLE
30	ITLNNSVALDPIDISIELNKAKSDLEE

ITLNNSVALDPIDISIELNKA KSDLEES
ITLNNSVALDPIDISIELNKA KSDLEESK
ITLNNSVALDPIDISIELNKA KSDLEESKE
ITLNNSVALDPIDISIELNKA KSDLEESKEW
5 ITLNNSVALDPIDISIELNKA KSDLEESKEWI
ITLNNSVALDPIDISIELNKA KSDLEESKEWIR
ITLNNSVALDPIDISIELNKA KSDLEESKEWIRR
ITLNNSVALDPIDISIELNKA KSDLEESKEWIRRS

10 The one letter amino acid code of Table 1 is used.

TABLE 13

HUMAN PARAINFLUENZA VIRUS 3 (HPV3) F1 REGION DPI78 ANALOG AMINO TRUNCATIONS	
5	RRS
	IRRS
	WIRRS
	EWIRRS
10	KEWIRRS
	SKEWIRRS
	ESKEWIRRS
	EESKEWIRRS
	LEESKEWIRRS
15	DLEESKEWIRRS
	SDLEESKEWIRRS
	KSDLEESKEWIRRS
	AKSDLEESKEWIRRS
	KAKSDLEESKEWIRRS
20	NKAKSDLEESKEWIRRS
	LNKAKSDLEESKEWIRRS
	ELNKAKSDLEESKEWIRRS
	IELNKAKSDLEESKEWIRRS
	SIELNKAKSDLEESKEWIRRS
25	ISIELNKAKSDLEESKEWIRRS
	DISIELNKAKSDLEESKEWIRRS
	IDISIELNKAKSDLEESKEWIRRS
	PIDISIELNKAKSDLEESKEWIRRS
	DPIDISIELNKAKSDLEESKEWIRRS
30	LDPIDISIELNKAKSDLEESKEWIRRS

ALDPIDISIELNKA KSDLEESKEWIRRS
VALDPIDISIELNKA KSDLEESKEWIRRS
SVALDPIDISIELNKA KSDLEESKEWIRRS
NSVALDPIDISIELNKA KSDLEESKEWIRRS
5 NNSVALDPIDISIELNKA KSDLEESKEWIRRS
LNNSVALDPIDISIELNKA KSDLEESKEWIRRS
TLNNSVALDPIDISIELNKA KSDLEESKEWIRRS

The one letter amino acid code of Table 1 is used.

TABLE 14

HUMAN PARAINFLUENZA VIRUS 3 (HPV3) F1 REGION	
DP107 ANALOG CARBOXY TRUNCATIONS	
5	
	ALG
	ALGV
	ALGVA
	ALGVAT
10	ALGVATS
	ALGVATSA
	ALGVATSAQ
	ALGVATSAQI
	ALGVATSAQIT
15	ALGVATSAQITA
	ALGVATSAQITAA
	ALGVATSAQITAAV
	ALGVATSAQITAAVA
	ALGVATSAQITAVAL
20	ALGVATSAQITAVALV
	ALGVATSAQITAVALVE
	ALGVATSAQITAVALVEA
	ALGVATSAQITAVALVEAK
	ALGVATSAQITAVALVEAKQ
25	ALGVATSAQITAVALVEAKQA
	ALGVATSAQITAVALVEAKQAR
	ALGVATSAQITAVALVEAKQARS
	ALGVATSAQITAVALVEAKQARSD
	ALGVATSAQITAVALVEAKQARSDI
30	ALGVATSAQITAVALVEAKQARSDIE

ALGVATSAQITA AVALVEAKQARSDIEK
ALGVATSAQITA AVALVEAKQARSDIEKL
ALGVATSAQITA AVALVEAKQARSDIEKLK
ALGVATSAQITA AVALVEAKQARSDIEKLKE
5 ALGVATSAQITA AVALVEAKQARSDIEKLKEA
ALGVATSAQITA AVALVEAKQARSDIEKLKEAI
ALGVATSAQITA AVALVEAKQARSDIEKLKEAIR

The one letter amino acid code of Table 1 is used.

TABLE 15

HUMAN PARAINFLUENZA VIRUS 3 (HPV3) F1 REGION	
DP107 ANALOG AMINO TRUNCATIONS	
5	IRD
	AIRD
	EAIRD
	KEAIRD
10	LKEAIRD
	KLKEAIRD
	EKLKEAIRD
	IEKLKEAIRD
	DIEKLKEAIRD
15	SDIEKLKEAIRD
	RSDIEKLKEAIRD
	ARSDIEKLKEAIRD
	QARSDIEKLKEAIRD
	KQARSDIEKLKEAIRD
20	AKQARSDIEKLKEAIRD
	EAKQARSDIEKLKEAIRD
	VEAKQARSDIEKLKEAIRD
	LVEAKQARSDIEKLKEAIRD
	ALVEAKQARSDIEKLKEAIRD
25	VALVEAKQARSDIEKLKEAIRD
	AVALVEAKQARSDIEKLKEAIRD
	AAVALVEAKQARSDIEKLKEAIRD
	TAAVALVEAKQARSDIEKLKEAIRD
	ITAAVALVEAKQARSDIEKLKEAIRD
30	QITAAVALVEAKQARSDIEKLKEAIRD

AQITA AVALVEAKQARSDIEKLKEAIRD
SAQITA AVALVEAKQARSDIEKLKEAIRD
TSAQITA AVALVEAKQARSDIEKLKEAIRD
ATSAQITA AVALVEAKQARSDIEKLKEAIRD
5 VATSAQITA AVALVEAKQARSDIEKLKEAIRD
GVATSAQITA AVALVEAKQARSDIEKLKEAIRD
LGVATSAQITA AVALVEAKQARSDIEKLKEAIRD

The one letter amino acid code of Table 1 is used.

TABLE 16

ANTI-RESPIRATORY SYNCYTIAL VIRUS (RSV) PEPTIDES

5	TSVITIELSNIKENKCNGTDAKVKLIKQELDKYKN SVITIELSNIKENKCNGTDAKVKLIKQELDKYKNA VITIELSNIKENKCNGTDAKVKLIKQELDKYKNAV VAVSKVLHLEGEVNKIALSTNKAVVSLSNGVS AVSKVLHLEGEVNKIALSTNKAVVSLSNGVSV
10	VSKVLHLEGEVNKIALSTNKAVVSLSNGVSVL SKVLHLEGEVNKIALSTNKAVVSLSNGVSVLT KVLHLEGEVNKIALSTNKAVVSLSNGVSVLTS LEGEVNKIALSTNKAVVSLSNGVSVLT SKVLD GEVNKIALSTNKAVVSLSNGVSVLT SKVLDLK
15	EVNKIALSTNKAVVSLSNGVSVLT SKVLDLKN VNKIALSTNKAVVSLSNGVSVLT SKVLDLKNY NKIALSTNKAVVSLSNGVSVLT SKVLDLKNYI KIALSTNKAVVSLSNGVSVLT SKVLDLKNYID IALSTNKAVVSLSNGVSVLT SKVLDLKNYIDK
20	ALLSTNKAVVSLSNGVSVLT SKVLDLKNYIDKQ VAVSKVLHLEGEVNKIALSTNKAVVSLSNGVS AVSKVLHLEGEVNKIALSTNKAVVSLSNGVSV VSKVLHLEGEVNKIALSTNKAVVSLSNGVSVL SKVLHLEGEVNKIALSTNKAVVSLSNGVSVLT
25	KVLHLEGEVNKIALSTNKAVVSLSNGVSVLTS LEGEVNKIALSTNKAVVSLSNGVSVLT SKVLD GEVNKIALSTNKAVVSLSNGVSVLT SKVLDLK EVNKIALSTNKAVVSLSNGVSVLT SKVLDLKN VNKIALSTNKAVVSLSNGVSVLT SKVLDLKNY
30	NKIALSTNKAVVSLSNGVSVLT SKVLDLKNYI

KIALSTNKAVVSLSNGVSVLTSKVLDLKNYID
IALSTNKAVVSLSNGVSVLTSKVLDLKNYIDK
ALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQ

- 5 The one letter amino acid code of Table 1 is used.

TABLE 17

 ANTI-HUMAN PARAINFLUENZA VIRUS 3 (HPV3) PEPTIDES

5	TLNNSVALDPIDISIELNKA	SDLEESKEWIRRSN
	LNNSVALDPIDISIELNKA	SDLEESKEWIRRSNQ
	NNSVALDPIDISIELNKA	SDLEESKEWIRRSNQK
	NSVALDPIDISIELNKA	SDLEESKEWIRRSNQKL
	SVALDPIDISIELNKA	SDLEESKEWIRRSNQKLD
10	VALDPIDISIELNKA	SDLEESKEWIRRSNQKLD
	ALDPIDISIELNKA	SDLEESKEWIRRSNQKLD
	LDPIDISIELNKA	SDLEESKEWIRRSNQKLD
	DPIDISIELNKA	SDLEESKEWIRRSNQKLD
	PIDISIELNKA	SDLEESKEWIRRSNQKLD
15	IDISIELNKA	SDLEESKEWIRRSNQKLD
	DISIELNKA	SDLEESKEWIRRSNQKLD
	ISIELNKA	SDLEESKEWIRRSNQKLD
	SIELNKA	SDLEESKEWIRRSNQKLD
	IELNKA	SDLEESKEWIRRSNQKLD
20	ELNKA	SDLEESKEWIRRSNQKLD
	TA	AVALEAKQARSDIEKLKEAIRDTNKAVQSVQS
	A	VALEAKQARSDIEKLKEAIRDTNKAVQSVQSSI
	L	VEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNL
	V	EAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI
25	E	AKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIV
	A	KQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA
	K	QARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAI
	Q	ARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIK
30	R	SDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSV

SDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQ
KLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVN
LKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNK
AIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEIV

5

The one letter amino acid code of Table 1 is used.

TABLE 18

ANTI-SIMIAN IMMUNODEFICIENCY VIRUS (SIV) PEPTIDES

5 WQEWERKVD FLEENITALLEEAQIQQEK NMYELQK
 QEWERKVD FLEENITALLEEAQIQQEK NMYELQKL
 EWERKVD FLEENITALLEEAQIQQEK NMYELQKLN
 WERKVD FLEENITALLEEAQIQQEK NMYELQKLNS
 ERKVD FLEENITALLEEAQIQQEK NMYELQKLNSW
10 RKVD FLEENITALLEEAQIQQEK NMYELQKLNSWD
 KVD FLEENITALLEEAQIQQEK NMYELQKLNSWDV
 VDFLEENITALLEEAQIQQEK NMYELQKLNSWDVF
 DFLEENITALLEEAQIQQEK NMYELQKLNSWDVFG
 FLEENITALLEEAQIQQEK NMYELQKLNSWDVFGN

15

The one letter amino acid code of Table 1 is used.

TABLE 19

ANTI-MEASLES VIRUS (MEV) PEPTIDES	
<hr/>	
5	LHRIDLGPISLERLDVGTNLGNIAIAKLEAKELL HRIDLGPISLERLDVGTNLGNIAIAKLEAKELLE RIDLGPISLERLDVGTNLGNIAIAKLEAKELLES IDLGPISLERLDVGTNLGNIAIAKLEAKELLESS DLGPISLERLDVGTNLGNIAIAKLEAKELLESSD
10	LGPPISLERLDVGTNLGNIAIAKLEAKELLESSDQ GPPISLERLDVGTNLGNIAIAKLEAKELLESSDQI PPISLERLDVGTNLGNIAIAKLEAKELLESSDQIL PISLERLDVGTNLGNIAIAKLEAKELLESSDQILR SLERLDVGTNLGNIAIAKLEAKELLESSDQILRSM
15	LERLDVGTNLGNIAIAKLEAKELLESSDQILRSMK

The one letter amino acid code of Table 1 is used.

We claim:

1. A modified anti-viral peptide comprising:
a peptide that exhibits anti-viral activity, and
5 a reactive group which is reactive with amino groups, hydroxyl groups, or thiol groups on blood components to form stable covalent bonds.
2. The modified peptide of claim 1 wherein said reactive group is a succinimidyl or a maleimido group.
10
3. The modified peptide of claim 1 wherein said reactive group is a maleimido group which is reactive with a thiol group on a blood protein.
4. The modified peptide of claim 1 wherein said peptide is DP178 or
15 DP107 or analogs thereof.
5. The modified peptide of claim 1 wherein said peptide exhibits anti-viral activity against human immunodeficiency virus (HIV).
- 20 6. The modified peptide of claim 5 wherein said peptide is selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:9.
7. The modified peptide of claim 5 wherein said peptide is DP 178 or DP 107.
25
8. The modified peptide of claim 1 wherein said peptide exhibits anti-viral activity against human respiratory syncytial virus (RSV).
9. The modified peptide of claim 8 wherein said peptide is selected
30 from the group consisting of SEQ ID NO:10 to SEQ ID NO:30.

10. The modified peptide of claim 8 wherein said peptide is selected from the group consisting of SEQ ID NO:14 to SEQ ID NO:17 and SEQ ID NO:29.

5

11. The modified peptide of claim 1 wherein said peptide exhibits anti-viral activity against human parainfluenza virus (HPIV).

12. The modified peptide of claim 11 wherein said peptide is selected from the group consisting of SEQ ID NO:31 to SEQ ID NO:62.

10

13. The modified peptide of claim 11 wherein said peptide is selected from the group consisting of SEQ ID NO: 35, SEQ ID NO:38 to SEQ ID NO:42, SEQ ID NO:52 and SEQ ID NO:58.

15

14. The modified peptide of claim 1 wherein said peptide exhibits anti-viral activity against measles virus (MeV).

15. The modified peptide of claim 14 wherein said peptide is selected from the group consisting of SEQ ID NO:74 to SEQ ID NO:86.

20

16. The modified peptide of claim 14 wherein said peptide is selected from the group consisting of SEQ ID NO:77, SEQ ID NO:79, SEQ ID NO:81 and SEQ ID NO:84.

25

17. The modified peptide of claim 1 wherein said peptide exhibits anti-viral activity against simian immunodeficiency virus (SIV).

18. The modified peptide of claim 17 wherein said peptide is selected from the group consisting of SEQ ID NO:63 to SEQ ID NO:73.

30

19. A composition for use in the prevention and/or treatment of acquired immune deficiency syndrome (AIDS) comprising a peptide that exhibits anti-viral activity against human immunodeficiency virus (HIV), modified with a reactive group which is reactive with amino groups, hydroxyl groups, or thiol groups on blood components to form stable covalent bonds.

20. The composition of claim 19 wherein said reactive group is a maleimido group which is reactive with a thiol group on a blood protein.

21. The composition of claim 20 wherein said peptide is DP178 or DP107 or analogs thereof.

22. A composition for use in the prevention and/or treatment of human respiratory syncytial virus (RSV) infection comprising a peptide that exhibits anti-viral activity against RSV, modified with a reactive group which is reactive with amino groups, hydroxyl groups, or thiol groups on blood components to form stable covalent bonds.

23. The composition of claim 22 wherein said reactive group is a maleimido group which is reactive with a thiol group on a blood protein.

24. The composition of claim 23 wherein said peptide is selected from the group consisting of SEQ ID NO:14 to SEQ ID NO:17 and SEQ ID NO:29.

25. A composition for use in the prevention and/or treatment of human parainfluenza virus (HPIV) infection comprising a peptide that exhibits anti-viral activity against human parainfluenza (HPIV), modified with a reactive group which is reactive with amino groups, hydroxyl groups, or thiol groups on blood components to form stable covalent bonds.

26. The composition of claim 25 wherein said reactive group is a maleimido group which is reactive with a thiol group on a blood protein.

5 27. The composition of claim 26 wherein said peptide is selected from the group consisting of SEQ ID NO: 35, SEQ ID NO:38 to SEQ ID NO:42, SEQ ID NO:52 and SEQ ID NO:58.

10 28. A composition for use in the prevention and/or treatment of measles virus (MeV) infection comprising a peptide that exhibits anti-viral activity against measles virus (MeV), modified with a reactive group which is reactive with amino groups, hydroxyl groups, or thiol groups on blood components to form stable covalent bonds.

15 29. The composition of claim 28 wherein said reactive group is a maleimido group which is reactive with a thiol group on a blood protein.

20 30. The composition of claim 29 wherein said peptide is selected from the group consisting of SEQ ID NO:77, SEQ ID NO:79, SEQ ID NO:81 and SEQ ID NO:84.

SEQUENCE LISTING

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<120> LONG LASTING FUSION PEPTIDE INHIBITORS OF VIRAL
INFECTION

<130> REDC-1510

<140>

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<150> US 60/134,406

<151> 1999-05-17

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1 5 10 15

Glu Lys Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu
20 25 30

Trp Asn Trp Phe
35

<210> 2

<211> 38

<212> PRT

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peptide

<400> 2

Asn Asn Leu Leu Arg Ala Ile Glu Ala Gln Gln His Leu Leu Gln Leu
1 5 10 15

Thr Val Trp Gln Ile Lys Gln Leu Gln Ala Arg Ile Leu Ala Val Glu
20 25 30

Arg Tyr Leu Lys Asp Gln
35

<210> 3

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peptide

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Tyr Thr Asn Thr Ile Tyr Thr Leu Leu Glu Glu Ser Gln Asn Gln Gln
1 5 10 15

Glu Lys Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu
20 25 30

Trp Asn Trp Phe
35

<210> 4

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peptide

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Tyr Thr Gly Ile Ile Tyr Asn Leu Leu Glu Glu Ser Gln Asn Gln Gln
1 5 10 15

Glu Lys Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Asn Leu

20 25 30

Trp Asn Trp Phe
35

<210> 5
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peptide

<400> 5
Tyr Thr Ser Leu Ile Tyr Ser Leu Leu Glu Lys Ser Gln Thr Gln Gln
1 5 10 15
Glu Lys Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu
20 25 30
Trp Asn Trp Phe
35

<210> 6
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
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peptide

<400> 6
Leu Glu Ala Asn Ile Ser Lys Ser Leu Glu Gln Ala Gln Ile Gln Gln
1 5 10 15
Glu Lys Asn Met Tyr Glu Leu Gln Lys Leu Asn Ser Trp Asp Ile Phe
20 25 30
Gly Asn Trp Phe
35

<210> 7
<211> 36

<212> PRT

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peptide

<400> 7

Leu Glu Ala Asn Ile Ser Gln Ser Leu Glu Gln Ala Gln Ile Gln Gln
1 5 10 15Glu Lys Asn Met Tyr Glu Leu Gln Lys Leu Asn Ser Trp Asp Val Phe
20 25 30Thr Asn Trp Leu
35

<210> 8

<211> 41

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
peptide

<400> 8

Cys Gly Gly Asn Asn Leu Leu Arg Ala Ile Glu Ala Gln Gln His Leu
1 5 10 15Leu Gln Leu Thr Val Trp Gly Ile Lys Gln Leu Gln Ala Arg Ile Leu
20 25 30Ala Val Glu Arg Tyr Leu Lys Asp Gln
35 40

<210> 9

<211> 38

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peptide

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Gln Gln Leu Leu Asp Val Val Lys Arg Gln Gln Glu Met Leu Arg Leu
1 5 10 15

Thr Val Trp Gly Thr Lys Asn Leu Gln Ala Arg Val Thr Ala Ile Glu
20 25 30

Lys Tyr Leu Lys Asp Gln
35

<210> 10

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peptide

<400> 10

Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Glu Asn Lys
1 5 10 15

Cys Asn Gly Ala Lys Val Lys Leu Ile Lys Gln Glu Leu Asp Lys Tyr
20 25 30

Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met Gln Ser Thr
35 40 45

<210> 11

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peptide

<400> 11

Ala Ser Gly Val Ala Val Ser Lys Val Leu His Leu Glu Gly Glu Val
1 5 10 15

Asn Lys Ile Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser
20 25 30

Asn Gly Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr
35 40 45

Ile Asp Lys Gln Leu Leu
50

<210> 12
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<212> PRT
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peptide

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Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro Leu Val Phe Pro Ser Asp
1 5 10 15
Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu Lys Ile Asn Gln Ser
20 25 30
Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu Leu His Asn Val Asn Ala
35 40 45

Gly Lys Ser Thr Thr
50

<210> 13
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peptide

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Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Glu Asn Lys
1 5 10 15
Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys Gln Glu Leu Asp
20 25 30
Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met Gln Ser Thr
35 40 45

<210> 14
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<212> PRT
<213> Artificial Sequence

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1 5 10 15
Cys Asn Gly Asp Ala Lys Val Lys Leu Ile Lys Gln Glu Leu Asp Lys
20 25 30
Tyr Lys

<210> 15
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peptide

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Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Glu Asn Lys Cys
1 5 10 15
Asn Gly Asp Ala Lys Val Lys Leu Ile Lys Gln Glu Leu Asp Lys Tyr
20 25 30
Lys Asn

<210> 16
<211> 34
<212> PRT
<213> Artificial Sequence

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peptide

<400> 16

Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Glu Asn Lys Cys Asn Gly
1 5 10 15Asp Ala Lys Val Lys Leu Ile Lys Gln Glu Leu Asp Lys Tyr Lys Asn
20 25 30

Ala Val

<210> 17

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<213> Artificial Sequence

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<223> Description of Artificial Sequence: synthetic
peptide

<400> 17

Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Glu Asn Lys Met Asn Gly
1 5 10 15Asp Ala Lys Val Lys Leu Ile Lys Gln Glu Leu Asp Lys Tyr Lys Asn
20 25 30

Ala Val

<210> 18

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<400> 18

Val Ala Val Ser Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile
1 5 10 15

Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val
20 25 30

Ser

<210> 19

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peptide

<400> 19

Ala Val Ser Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Ala
1 5 10 15

Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser
20 25 30

Val

<210> 20

<211> 33

<212> PRT

<213> Artificial Sequence

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peptide

<400> 20

Val Ser Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Ala Leu
1 5 10 15

Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val
20 25 30

Leu

<210> 21

<211> 33
<212> PRT
<213> Artificial Sequence

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peptide

<400> 21

Ser Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Ala Leu Leu
1 5 10 15

Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu
20 25 30

Thr

<210> 22
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peptide

<400> 22

Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Ala Leu Leu Ser
1 5 10 15

Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr
20 25 30

Ser

<210> 23
<211> 33
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 23

Leu Glu Gly Glu Val Asn Lys Ile Ala Leu Leu Ser Thr Asn Lys Ala
1 5 10 15

Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val Leu
20 25 30

Asp

<210> 24

<211> 33

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 24

Gly Glu Val Asn Lys Ile Ala Leu Leu Ser Thr Asn Lys Ala Val Val
1 5 10 15

Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu
20 25 30

Lys

<210> 25

<211> 33

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 25

Glu Val Asn Lys Ile Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser
1 5 10 15

Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys
20 25 30

Asn

<210> 26
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 26
Val Asn Lys Ile Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu
1 5 10 15
Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn
20 25 30

Tyr

<210> 27
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 27
Asn Lys Ile Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser
1 5 10 15
Asn Gly Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr
20 25 30

Ile

<210> 28
<211> 33
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 28

Lys Ile Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn
1 5 10 15Gly Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile
20 25 30

Asp

<210> 29

<211> 33

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 29

Ile Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly
1 5 10 15Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp
20 25 30

Lys

<210> 30

<211> 33

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 30

Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val
1 5 10 15

Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp Lys
 20 25 30

Gln

<210> 31

<211> 70

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
 peptide

<400> 31

Gly Thr Ile Ala Leu Gly Val Ala Thr Ser Ala Gln Ile Thr Ala Ala
 1 5 10 15

Val Ala Leu Val Glu Ala Lys Gln Ala Arg Ser Asp Ile Glu Lys Leu
 20 25 30

Lys Glu Ala Ile Arg Asp Thr Asn Lys Ala Val Gln Ser Val Gln Ser
 35 40 45

Ser Ile Gly Asn Leu Ile Val Ala Ile Lys Ser Val Gln Asp Tyr Val
 50 55 60

Asn Lys Glu Ile Val Pro
 65 70

<210> 32

<211> 56

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
 peptide

<400> 32

Tyr Thr Pro Asn Asp Ile Thr Leu Asn Asn Ser Val Ala Leu Asp Pro
 1 5 10 15

Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys Ser Asp Leu Glu Glu
 20 25 30

Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys Leu Asp Ser Ile Gly
35 40 45

Asn Trp His Gln Ser Ser Thr Thr
50 55

<210> 33

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 33

Thr Leu Asn Asn Ser Val Ala Leu Asp Pro Ile Asp Ile Ser Ile Glu
1 5 10 15

Leu Asn Lys Ala Lys Ser Asp Leu Glu Glu Ser Lys Glu Trp Ile Arg
20 25 30

Arg Ser Asn
35

<210> 34

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 34

Leu Asn Asn Ser Val Ala Leu Asp Pro Ile Asp Ile Ser Ile Glu Leu
1 5 10 15

Asn Lys Ala Lys Ser Asp Leu Glu Glu Ser Lys Glu Trp Ile Arg Arg
20 25 30

Ser Asn Gln
35

<210> 35

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic peptide

<400> 35

Asn Asn Ser Val Ala Leu Asp Pro Ile Asp Ile Ser Ile Glu Leu Asn
1 5 10 15

Lys Ala Lys Ser Asp Leu Glu Glu Ser Lys Glu Trp Ile Arg Arg Ser
20 25 30

Asn Gln Lys
35

<210> 36

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic peptide

<400> 36

Asn Ser Val Ala Leu Asp Pro Ile Asp Ile Ser Ile Glu Leu Asn Lys
1 5 10 15

Ala Lys Ser Asp Leu Glu Glu Ser Lys Glu Trp Ile Arg Arg Ser Asn
20 25 30

Gln Lys Leu
35

<210> 37

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic peptide

<400> 37

Ser Val Ala Leu Asp Pro Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala
1 5 10 15

Lys Ser Asp Leu Glu Glu Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln
20 25 30

Lys Leu Asp
35

<210> 38

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 38

Val Ala Leu Asp Pro Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys
1 5 10 15

Ser Asp Leu Glu Glu Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys
20 25 30

Leu Asp Ser
35

<210> 39

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 39

Ala Leu Asp Pro Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys Ser
1 5 10 15

Asp Leu Glu Glu Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys Leu
20 25 30

Asp Ser Ile
35

<210> 40
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 40
Leu Asp Pro Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys Ser Asp
1 5 10 15
Leu Glu Glu Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys Leu Asp
20 25 30

Ser Ile Gly
35

<210> 41
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 41
Asp Pro Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys Ser Asp Leu
1 5 10 15
Glu Glu Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys Leu Asp Ser
20 25 30

Ile Gly Asn
35

<210> 42
<211> 35
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 42

Pro Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys Ser Asp Leu Glu
1 5 10 15Glu Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys Leu Asp Ser Ile
20 25 30Gly Asn Trp
35

<210> 43

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 43

Ile Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys Ser Asp Leu Glu Glu
1 5 10 15Ser Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys Leu Asp Ser Ile Gly
20 25 30Asn Trp His
35

<210> 44

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 44

Asp Ile Ser Ile Glu Leu Asn Lys Ala Lys Ser Asp Leu Glu Glu Ser
1 5 10 15

Lys Glu Trp Ile Arg Arg Ser Asn Gln Lys Leu Asp Ser Ile Gly Asn
20 25 30

Trp His Gln
35

<210> 45

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 45

Ile Ser Ile Glu Leu Asn Lys Ala Lys Ser Asp Leu Glu Glu Ser Lys
1 5 10 15

Glu Trp Ile Arg Arg Ser Asn Gln Lys Leu Asp Ser Ile Gly Asn Trp
20 25 30

His Gln Ser
35

<210> 46

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 46

Ser Ile Glu Leu Asn Lys Ala Lys Ser Asp Leu Glu Glu Ser Lys Glu
1 5 10 15

Trp Ile Arg Arg Ser Asn Gln Lys Leu Asp Ser Ile Gly Asn Trp His
20 25 30

Gln Ser Ser
35

<210> 47
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 47
Ile Glu Leu Asn Lys Ala Lys Ser Asp Leu Glu Glu Ser Lys Glu Trp
1 5 10 15
Ile Arg Arg Ser Asn Gln Lys Leu Asp Ser Ile Gly Asn Trp His Gln
20 25 30
Ser Ser Thr
35

<210> 48
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 48
Glu Leu Asn Lys Ala Lys Ser Asp Leu Glu Glu Ser Lys Glu Trp Ile
1 5 10 15
Arg Arg Ser Asn Gln Lys Leu Asp Ser Ile Gly Asn Trp His Gln Ser
20 25 30
Ser Thr Thr
35

<210> 49
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 49

Thr Ala Ala Val Ala Leu Val Glu Ala Lys Gln Ala Arg Ser Asp Ile
1 5 10 15

Glu Lys Leu Lys Glu Ala Ile Arg Asp Thr Asn Lys Ala Val Gln Ser
20 25 30

Val Gln Ser
35

<210> 50

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 50

Ala Val Ala Leu Val Glu Ala Lys Gln Ala Arg Ser Asp Ile Glu Lys
1 5 10 15

Leu Lys Glu Ala Ile Arg Asp Thr Asn Lys Ala Val Gln Ser Val Gln
20 25 30

Ser Ser Ile
35

<210> 51

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 51

Leu Val Glu Ala Lys Gln Ala Arg Ser Asp Ile Glu Lys Leu Lys Glu
1 5 10 15

Ala Ile Arg Asp Thr Asn Lys Ala Val Gln Ser Val Gln Ser Ser Ile
20 25 30

Gly Asn Leu
35

<210> 52
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 52
Val Glu Ala Lys Gln Ala Arg Ser Asp Ile Glu Lys Leu Lys Glu Ala
1 5 10 15
Ile Arg Asp Thr Asn Lys Ala Val Gln Ser Val Gln Ser Ser Ile Gly
20 25 30

Asn Leu Ile
35

<210> 53
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 53
Glu Ala Lys Gln Ala Arg Ser Asp Ile Glu Lys Leu Lys Glu Ala Ile
1 5 10 15
Arg Asp Thr Asn Lys Ala Val Gln Ser Val Gln Ser Ser Ile Gly Asn
20 25 30

Leu Ile Val
35

<210> 54
<211> 35
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 54

Ala Lys Gln Ala Arg Ser Asp Ile Glu Lys Leu Lys Glu Ala Ile Arg
1 5 10 15Asp Thr Asn Lys Ala Val Gln Ser Val Gln Ser Ser Ile Gly Asn Leu
20 25 30Ile Val Ala
35

<210> 55

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 55

Lys Gln Ala Arg Ser Asp Ile Glu Lys Leu Lys Glu Ala Ile Arg Asp
1 5 10 15Thr Asn Lys Ala Val Gln Ser Val Gln Ser Ser Ile Gly Asn Leu Ile
20 25 30Val Ala Ile
35

<210> 56

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 56

Gln Ala Arg Ser Asp Ile Glu Lys Leu Lys Glu Ala Ile Arg Asp Thr
1 5 10 15

Asn Lys Ala Val Gln Ser Val Gln Ser Ser Ile Gly Asn Leu Ile Val
20 25 30

Ala Ile Lys
35

<210> 57

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 57

Ala Arg Ser Asp Ile Glu Lys Leu Lys Glu Ala Ile Arg Asp Thr Asn
1 5 10 15

Lys Ala Val Gln Ser Val Gln Ser Ser Ile Gly Asn Leu Ile Val Ala
20 25 30

Ile Lys Ser
35

<210> 58

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 58

Arg Ser Asp Ile Glu Lys Leu Lys Glu Ala Ile Arg Asp Thr Asn Lys
1 5 10 15

Ala Val Gln Ser Val Gln Ser Ser Ile Gly Asn Leu Ile Val Ala Ile
20 25 30

Lys Ser Val
35

<210> 59

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 59

Ser Asp Ile Glu Lys Leu Lys Glu Ala Ile Arg Asp Thr Asn Lys Ala
1 5 10 15

Val Gln Ser Val Gln Ser Ser Ile Gly Asn Leu Ile Val Ala Ile Lys
20 25 30

Ser Val Gln
35

<210> 60

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 60

Lys Leu Lys Glu Ala Ile Arg Asp Thr Asn Lys Ala Val Gln Ser Val
1 5 10 15

Gln Ser Ser Ile Gly Asn Leu Ile Val Ala Ile Lys Ser Val Gln Asp
20 25 30

Tyr Val Asn
35

<210> 61

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 61

Leu Lys Glu Ala Ile Arg Asp Thr Asn Lys Ala Val Gln Ser Val Gln
1 5 10 15

Ser Ser Ile Gly Asn Leu Ile Val Ala Ile Lys Ser Val Gln Asp Tyr
20 25 30

Val Asn Lys
35

<210> 62

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 62

Ala Ile Arg Asp Thr Asn Lys Ala Val Gln Ser Val Gln Ser Ser Ile
1 5 10 15

Gly Asn Leu Ile Val Ala Ile Lys Ser Val Gln Asp Tyr Val Asn Lys
20 25 30

Glu Ile Val
35

<210> 63

<211> 47

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 63

Thr Trp Gln Glu Trp Glu Arg Lys Val Asp Phe Leu Glu Glu Asn Ile
1 5 10 15

Thr Ala Leu Leu Glu Glu Ala Gln Ile Gln Gln Glu Lys Asn Met Tyr
20 25 30

Glu Leu Gln Lys Leu Asn Ser Trp Asp Val Phe Gly Asn Trp Phe
 35 40 45

<210> 64
 <211> 35
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: synthetic
 peptide

<400> 64
 Trp Gln Glu Trp Glu Arg Lys Val Asp Phe Leu Glu Glu Asn Ile Thr
 1 5 10 15

Ala Leu Leu Glu Glu Ala Gln Ile Gln Gln Glu Lys Asn Met Tyr Glu
 20 25 30

Leu Gln Lys
 35

<210> 65
 <211> 35
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: synthetic
 peptide

<400> 65
 Gln Glu Trp Glu Arg Lys Val Asp Phe Leu Glu Glu Asn Ile Thr Ala
 1 5 10 15

Leu Leu Glu Glu Ala Gln Ile Gln Gln Glu Lys Asn Met Tyr Glu Leu
 20 25 30

Gln Lys Leu
 35

<210> 66
 <211> 35
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic peptide

<400> 66

Glu Trp Glu Arg Lys Val Asp Phe Leu Glu Glu Asn Ile Thr Ala Leu
1 5 10 15

Leu Glu Glu Ala Gln Ile Gln Gln Glu Lys Asn Met Tyr Glu Leu Gln
20 25 30

Lys Leu Asn
35

<210> 67

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic peptide

<400> 67

Trp Glu Arg Lys Val Asp Phe Leu Glu Glu Asn Ile Thr Ala Leu Leu
1 5 10 15

Glu Glu Ala Gln Ile Gln Gln Glu Lys Asn Met Tyr Glu Leu Gln Lys
20 25 30

Leu Asn Ser
35

<210> 68

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic peptide

<400> 68

Glu Arg Lys Val Asp Phe Leu Glu Glu Asn Ile Thr Ala Leu Leu Glu
1 5 10 15

Glu Ala Gln Ile Gln Gln Glu Lys Asn Met Tyr Glu Leu Gln Lys Leu
 20 25 30

Asn Ser Trp
 35

<210> 69
 <211> 35
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: synthetic
 peptide

<400> 69
 Arg Lys Val Asp Phe Leu Glu Glu Asn Ile Thr Ala Leu Leu Glu Glu
 1 5 10 15

Ala Gln Ile Gln Gln Glu Lys Asn Met Tyr Glu Leu Gln Lys Leu Asn
 20 25 30

Ser Trp Asp
 35

<210> 70
 <211> 35
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: synthetic
 peptide

<400> 70
 Lys Val Asp Phe Leu Glu Glu Asn Ile Thr Ala Leu Leu Glu Glu Ala
 1 5 10 15

Gln Ile Gln Gln Glu Lys Asn Met Tyr Glu Leu Gln Lys Leu Asn Ser
 20 25 30

Trp Asp Val
 35

<210> 71
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 71
Val Asp Phe Leu Glu Glu Asn Ile Thr Ala Leu Leu Glu Glu Ala Gln
1 5 10 15
Ile Gln Gln Glu Lys Asn Met Tyr Glu Leu Gln Lys Leu Asn Ser Trp
20 25 30
Asp Val Phe
35

<210> 72
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 72
Asp Phe Leu Glu Glu Asn Ile Thr Ala Leu Leu Glu Glu Ala Gln Ile
1 5 10 15
Gln Gln Glu Lys Asn Met Tyr Glu Leu Gln Lys Leu Asn Ser Trp Asp
20 25 30
Val Phe Gly
35

<210> 73
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 73

Phe Leu Glu Glu Asn Ile Thr Ala Leu Leu Glu Glu Ala Gln Ile Gln
1 5 10 15

Gln Glu Lys Asn Met Tyr Glu Leu Gln Lys Leu Asn Ser Trp Asp Val
20 25 30

Phe Gly Asn

35

<210> 74

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 74

Pro Asp Ala Val Tyr Leu His Arg Ile Asp Leu Gly Pro Pro Ile Ser
1 5 10 15

Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly Asn Ala Ile Ala Lys
20 25 30

Leu Glu Asp

35

<210> 75

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 75

Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly Asn Ala Ile Ala Lys
1 5 10 15

Leu Glu Ala Lys Glu Leu Leu Glu Ser Ser Asp Gln Ile Leu Arg Ser
20 25 30

Met Lys

<210> 76

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 76

Leu His Arg Ile Asp Leu Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp
1 5 10 15

Val Gly Thr Asn Leu Gly Asn Ala Ile Ala Lys Leu Glu Ala Lys Glu
20 25 30

Leu Leu

<210> 77

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 77

His Arg Ile Asp Leu Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp Val
1 5 10 15

Gly Thr Asn Leu Gly Asn Ala Ile Ala Lys Leu Glu Ala Lys Glu Leu
20 25 30

Leu Glu

<210> 78

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 78

Arg Ile Asp Leu Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp Val Gly
1 5 10 15Thr Asn Leu Gly Asn Ala Ile Ala Lys Leu Glu Ala Lys Glu Leu Leu
20 25 30

Glu Ser

<210> 79

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 79

Ile Asp Leu Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp Val Gly Thr
1 5 10 15Asn Leu Gly Asn Ala Ile Ala Lys Leu Glu Ala Lys Glu Leu Leu Glu
20 25 30

Ser Ser

<210> 80

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 80

Asp Leu Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp Val Gly Thr Asn
1 5 10 15

Leu Gly Asn Ala Ile Ala Lys Leu Glu Ala Lys Glu Leu Leu Glu Ser
20 25 30

Ser Asp

<210> 81

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 81

Leu Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp Val Gly Thr Asn Leu
1 5 10 15

Gly Asn Ala Ile Ala Lys Leu Glu Ala Lys Glu Leu Leu Glu Ser Ser
20 25 30

Asp Gln

<210> 82

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 82

Gly Pro Pro Ile Ser Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly
1 5 10 15

Asn Ala Ile Ala Lys Leu Glu Ala Lys Glu Leu Leu Glu Ser Ser Asp
20 25 30

Gln Ile

<210> 83
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 83
Pro Pro Ile Ser Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly Asn
1 5 10 15

Ala Ile Ala Lys Leu Glu Ala Lys Glu Leu Leu Glu Ser Ser Asp Gln
20 25 30

Ile Leu

<210> 84
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 84
Pro Ile Ser Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly Asn Ala
1 5 10 15

Ile Ala Lys Leu Glu Ala Lys Glu Leu Leu Glu Ser Ser Asp Gln Ile
20 25 30

Leu Arg

<210> 85
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic
peptide

<400> 85

Ser Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly Asn Ala Ile Ala
1 5 10 15

Lys Leu Glu Ala Lys Glu Leu Leu Glu Ser Ser Asp Gln Ile Leu Arg
20 25 30

Ser Met

<210> 86

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic
peptide

<400> 86

Leu Glu Arg Leu Asp Val Gly Thr Asn Leu Gly Asn Ala Ile Ala Lys
1 5 10 15

Leu Glu Ala Lys Glu Leu Leu Glu Ser Ser Asp Gln Ile Leu Arg Ser
20 25 30

Met Lys

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/13651

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/115 C07K14/135 C07K14/155 C07K14/16 A61K38/16
A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 10302 A (REDCELL INC) 20 April 1995 (1995-04-20) claims; example 3 ---	1-3, 19, 20
A	EP 0 602 290 A (POULETTY PHILIPPE ;POULETTY CHRISTINE (US)) 22 June 1994 (1994-06-22) column 5, line 32 - line 53; claims column 6, line 44 - line 55 ---	1-3, 19, 20
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Further documents are listed in the continuation of box C.



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Date of the actual completion of the international search

12 October 2000

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19/10/2000

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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